National Guidelines for Drug Susceptible Tuberculosis

2019 Edition

Ministry of Health
Government of Lesotho
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Foreword

The Ministry of Health through the National TB and Leprosy Programme (NTLP) continue to make commendable milestones in the fight against TB. The adoption of the Direct Observation Treatment Strategy in the 1990s, further strengthened by the Stop TB strategy in the latter years have been instrumental in achieving relatively better treatment outcomes. The new and ambitious End TB strategy which is well aligned with United Nations Sustainable Goals (SDGs) is a clear indication of the global efforts too. This is supported by numerous innovations and advances in technologies introduction of fixed drug combinations (FDCs) since 2009 to improve treatment adherence and molecular testing for TB through Xpert MTB.

The commitment of the Government of Lesotho end TB as a public health problem has resulted in strengthening the NTLP at both national and district levels following the 2004, 2010 and 2017 external reviews of the TB Programme. The efforts of the Government of Lesotho have been enhanced through strong partnerships between Government of Lesotho (GoL) and Christian Health Association of Lesotho (CHAL) which owns almost half of the facilities, World Health Organization (WHO), Partners In Health (PIH), Centres for Disease Control and Prevention (CDC), International Centre for AIDS Care and Treatment Program (ICAP), Elizabeth Glazier Paediatric AIDS Foundation (EGPAF), Baylor, Solidarmed, and others which enabled rapid expansion of access to TB diagnostic and treatment services. The efforts by in country Civil Society Organizations and Non-Governmental Associations have been of benefit in reaching out to the communities with TB services.

This National Tuberculosis guidelines of 2019 come shortly after the Global Ministerial Conference to "Ending TB in the Sustainable Development Era: A Multisectoral Response" held in Moscow, Russian Federation, in November 2017 and the release of the Moscow Declaration followed by the political declaration from United National High Level Meeting (UNHLM) in 2018. Implementation of this should be a meticulous one in order to achieve all the national and global goals to end TB. The guidelines should direct all actions in finding the missing TB cases, their management, care and support even for the vulnerable groups such as miners and ex-miners, Health Care Workers, children and People Living with HIV.

I would like to acknowledge all those who contributed in the revision and publication of this edition and those who continue to fund their implementation. TB is a public health concerns in Lesotho, hence the need for the National Tuberculosis and HIV/AIDS Programmes of Lesotho together with partners and private sector to be adequately prepared to deal with the challenges of ending TB in the midst of HIV. Proper implementation of the newly revised guidelines has the potential to reduce the incidence, improve treatment outcomes; therefore, the Ministry of Health urges all the clinicians to adhere to them.

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Mr. Nkaku Kabi
Honourable Minister of Health

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Executive Summary

The World Health Organization (WHO) in 2012 estimated that globally 8.7 million incident cases of TB occurred in 2011 (13% HIV co-infection). There were also 1.4 million deaths from TB (990 000 deaths among HIV-negative individuals and 430 000 among HIV-positive). These deaths included 0.5 million women, making TB one of the top killers of women worldwide[1].

Tuberculosis (TB) has risen markedly in sub-Saharan African nations over the past 2 decades, with reported annual incidence doubling between 1990 and 2007. The most recent estimates of TB data from the WHO indicate that TB incidence declined in only 10 of 46 African countries between 2000 and 2007. The African Region has 24% of the world's cases and the highest rates of cases and deaths per capita.

The 15 countries of the Southern African Development Community (SADC) region also include five of the 22 global TB high-burden countries identified by the WHO. The SADC region has some of the highest national adult HIV prevalence rates in the world, and accounts for more than 37% of all people living with HIV.

Lesotho is one of the fifteen countries with highest per capita case incidence 632/100,000 (WHO Global Tuberculosis Report 2012). Although notifications remain high, trends in the past five years evidence noticeable steady stabilization with slight decline. A total of 11,971 patients were notified in 2012 compared to 13,520 recorded in 2009. The TB burden in Lesotho remains huge. All forms of TB (new and previously treated) have continued to show a linear increase from 1990 onwards with only a slight decline since 2007. Furthermore, TB notification rates have remained above 400 per 100,000 population.

In Lesotho, TB is associated with HIV co-infection, social concerns, difficulties in patient adherence and the threat of resistance against anti-tuberculosis drugs. Lesotho has the third highest adult HIV prevalence in the world at 23%. There are an estimated 62 new HIV infections and 50 deaths due to AIDS each day in the country. An estimated 270,000 people are living with HIV in Lesotho as of end 2007 of which 11,801 are infected children while 258,472 are infected adults. Other factors favouring transmission of *M. tuberculosis* infection and progression to disease include poverty, overcrowding, poor ventilation, alcoholism and poor nutrition.

The guidelines give clear guidance to Health Workers in provision of efficient, effective and high-quality TB care and treatment at all service delivery points. This will enhance overall clinical performance since they will be armed with new knowledge and skills. This edition has adopted the new case definitions which accommodate all the available diagnostics in the country, the newly released WHO guidelines (most recommendations of which Lesotho had already been implementing) and the 2010 rapid advice in Treatment of TB in Children. New chapters on Addressing Mycobacterium Other Than TB (MOTT), Adherence and Psycho Social issues, Logistics and Drug Management, etc. were added to this version and have incorporated the Three Is (Intensified Case Finding ICF, Isoniazid Preventive Therapy-IPT and Infection Control-IC) of Tuberculosis Control in high-HIV prevalence settings.

[1] Global Tuberculosis Report 2012. WHO, 2012. WHO/HTM/TB/2012.6 <http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf>

Abbreviations and Acronyms

AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
BCG	Bacillus Calmette-Guerin
CTX	Cotrimoxazole
CXR	Chest x-ray
DS TB	Drug Susceptible Tuberculosis
EPTB	Extra-pulmonary tuberculosis
HCW	Health care worker
HIV	Human Immunodeficiency Virus
HTC	HIV Testing and Counselling
IC	Infection Control
ICF	Intensified Case Finding
IPT	Isoniazid Preventive Therapy
M&E	Monitoring and evaluation
MDR-TB	Multi-drug resistant tuberculosis
MOTT	Mycobacterium other than TB
NGO	Non-governmental organization
PLHIV	People living with HIV
PTB	Pulmonary tuberculosis
RR-TB	Rifampicin-resistant tuberculosis
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis

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TB Case Definitions

Purposes of Defining a TB Case

In order to compare data within our program, standard case definitions are used to categorize patients. This also allows comparison with other programs across countries and regions. Standard definition in use by Lesotho are adapted from international governing bodies such as the WHO.

Lesotho adopted the use of WHO-approved molecular diagnosis tests in addition to traditional microscopy to improve diagnosis and management of TB in both children and adults several years ago. Previous treatment guidelines, case definitions and treatment outcomes do not readily incorporate these technological advances. Therefore, case definitions, resistance classifications and treatment outcomes have all been updated.

Case Definitions

Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB.

A bacteriological confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics. All such cases should be notified regardless of whether TB treatment has started or not.

A clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the bases of x-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive should be reclassified as bacteriologically confirmed.

Classification of TB According to the Anatomical Site

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and /or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary TB.

Extra pulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

A patient with both PTB and EPTB should be classified as a pulmonary case.

Classification Based on History of Previous Treatment

Table 1: Classification based on history of previous treatment

Classification	Definition
New Patients	Have never had treatment for TB or those who have taken TB medications for less than one month
Previously treated	Have received TB treatment for a month or more in the past. Further classified by outcome of the most recent course of treatment. **Relapse:** patients have previously been treated for TB, were declared *cured* or *treatment completed* at the end of their most recent course of treatment and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection). **Treatment after failure:** patients have previously been treated for TB and their treatment failed at the end of the most recent course of treatment. **Treatment after lost to follow-up:** patients have previously been treated for TB and were declared *lost to follow-up* (treatment interrupted for 2 consecutive months or more) at the end of their most recent course of treatment. **Other previously treated:** patients have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.
Unknown	Do not fit into any of the categories of treatment history above

Classification based on HIV status

Table 2: Classification based on HIV status

HIV status	Definition
HIV Positive TB Patient	Any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing (conducted at the time of TB diagnosis or other documented evidence of HIV infection)
HIV Negative TB Patient	Any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified as an HIV-positive TB patient.
HIV status unknown TB Patient	Any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no documented evidence of enrolment into HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

Classification Based on Drug Resistance

Table 3: Classification based on drug resistance

Classification	Definition
Mono-resistance	Resistance to one first-line TB medication
Poly- drug resistance	Resistance to more than one first-line TB medication other than both INH and RIF

Classification	Definition
MDR-TB	Resistance to at least both INH and RIF
XDR-TB	Resistance to any flouroquinolone and any second-line injectable drugs, in addition to MDR
Rifampicin Resistance (RRTB)	Resistance to RIF detected using phenotyping and genotyping methods with or without resistance to other anti-TB drugs.[i]

These categories are not all mutually exclusive. When enumerating rifampicin-resistant TB (RR-TB), multidrug-resistant TB and extensively drug-resistant TB are also included.

Treatment Outcomes for patients with Drug-Susceptible TB

Drug susceptible TB patients in this section refers to patients who do not have evidence of infection with strains resistant to rifampicin. All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome.

Table 4: Treatment outcomes for drug-susceptible TB

Outcome	Definitions
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion
Treatment completed	A TB patient who completed treatment without evidence of failure but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion
Treatment failed	A TB patient whose sputum smear or culture is positive at 5 months or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases transferred out to another treatment unit as well as cases for whom the treatment outcome is unknown.
Treatment success	The sum of *cured* and *treatment completed.*

Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort and included only in the drug-resistant TB treatment cohort analysis.

Treatment outcomes for drug-resistant TB

These outcomes apply to patients with RR-TB, MDR-TB, XDR-TB who are treated using second-line treatment.

Table 5: Treatment outcomes for drug-resistant TB

Outcome	Definitions
Cured	Treatment completed as recommended by national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment	Treatment completed as recommended by national policy without evidence of failure BUT

completed	no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment failed	Treatment terminated or need for permanent regimen change of at least two TB medications due to: - Lack of conversion[a] by the end of the intensive phase *or* - Bacteriologic reversion[b] in the continuations phase after conversion to negative *or* - Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs *or* - Adverse drug reactions
Died	Patient who dies for any reason during the course of treatment
Lost to follow-up	Patient whose treatment was interrupted for two consecutive months or more
Not Evaluated	Patient for whom no treatment outcome is assigned.
Treatment success	The sum of *cured* and *treatment completed*

Diagnosis of Pulmonary TB

Approach to PTB diagnosis

Diagnosis is perhaps the critical step in control and management of TB. Active case finding of infectious TB patients and effective treatment to achieve cure with quality assured TB medications is the best public health approach to break the chain of transmission of tubercle bacilli and improve the epidemiological situation of TB in the country. Therefore, all persons (regardless of HIV status) with clinical features suggestive of PTB must submit sputum for bacteriological diagnosis (GeneXpert, culture). In Lesotho around 70 -73% of TB patients who know their HIV status are HIV positive. These are likely to have EPTB making the diagnosis of TB more difficult.

Clinical Presentation of Pulmonary TB

Over 90% of patients with PTB develop a cough soon after disease onset. The most common symptoms of pulmonary tuberculosis are:

- Cough
    - Persistent cough for 2 weeks or more; every patient presenting to a health facility with this symptom should be designated a "Presumptive TB case"
- Fever
- Night sweats
- Weight loss

Other features to look out for include:

- Sputum production which may be blood-stained (hemoptysis)
- General non-specific symptoms such as shortness of breath, chest pain, a general feeling of illness (malaise), tiredness, and loss of appetite

Cough and fever of any duration in an HIV patient should prompt an evaluation for TB

Several factors increase risk of TB. These include age, previous exposure to a TB case, history of previous treatment, HIV infection and other immuno-suppressive conditions, occupational contexts (especially in the mining industry, health care workers, etc.), duration since infection was acquired, smoking and alcohol consumption.

Physical examination

The physical signs in patients with PTB are often non-specific and in co-infected individuals may be caused by other HIV related illnesses. Possible findings include fever, wasting, enlarged lymph-nodes, pleural effusion, tachycardia and dyspnoea.

Lung examination

Lung exams do not help distinguish PTB from other chest diseases. Chest signs may include crackles, wheezes, bronchial breathing and diminished breath sounds. There are often no abnormal signs in the chest.

All presumptive TB cases who present to health facilities should be recorded in the TB screening and detection Register.

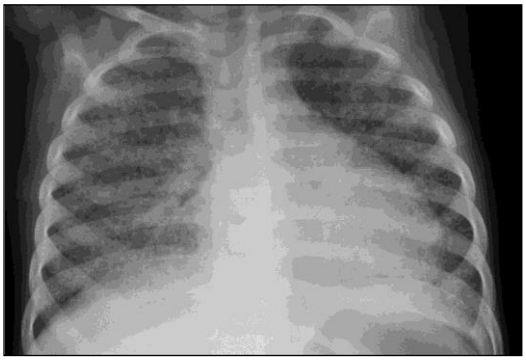
Clinical Presentation of Miliary TB

Miliary TB is the widespread dissemination of TB via hematogenous means. It is classically seen as millet-like infiltrates in the lungs on chest x-ray (Fig 1). In almost all cases, the organism is disseminated throughout the body, including the brain, with up to 25% of adult cases having meningeal involvement. Associated TB meningitis is even higher in young children.

Miliary TB often presents with non-specific clinical features such as: fever, fatigue, weakness and cough. Generalized lymphadenopathy, mildly-enlarged liver and spleen, and rapid weight loss are among some of the associated signs. Given the high mortality associated with miliary TB and a non-specific clinical presentation, a high index of clinical suspicion is important in obtaining an early diagnosis and initiating immediate treatment. Sputum examinations are usually negative and CXR remains a key diagnostic tool. Miliary TB is more frequent in immunocompromised patients and children and an under-diagnosed cause of end-stage wasting in HIV-infected individuals and should be considered in all febrile clients presenting with HIV wasting syndrome.

Without treatment, the mortality from miliary TB is almost 100%. Prompt initiation of TB treatment dramatically alters the course of disease, reducing mortality to less than 10% with most deaths occurring within the first two weeks of diagnosis. Miliary TB is a medical emergency and treatment should begin immediately in all presumptive cases.

Figure 1: Miliary TB. Note the millet sized opacities uniformly distributed in both lungs.



Sputum Collection, Labelling, Storage and Transport

All presumptive TB cases should produce at least two sputum specimens.

During the first encounter, the first specimen is collected on the spot and referred to as the **"spot specimen"**; the patient should be provided with a sputum container for collection of the second sample early morning at home **('early morning specimen')**.

In the case whereby the patient is unable to bring early morning sample, two spot samples may be collected, but should be 2 hours apart.

All facilities should have a sputum collection booth within their premises in a well ventilated location away from other patients to facilitate spot specimen collection

Sputum collection procedure

Regularly, show video on sputum collection in the facility to enhance patient's knowledge on how to provide good quality specimen

- Sputum collection should be supervised; good quality of sputum increases chances of good yield
- Do it in a designated point within the facility
- Explain the steps fully and slowly and demonstrate deep cough clearly from the bottom of the chest, beginning with deep breathing
- Do not stand in front of the patient
- The patient should rinse the mouth with water prior to production of sputum
- Ask the patient to be very careful to direct the sputum into the container not to contaminate the outside of it.
- Wear gloves
- Give the patient the container without the lid
- Hold the lid, ready to replace it immediately
- Make sure that the lid is securely closed
- Remove gloves and wash hands after handling the sputum specimen
- Provide early morning sample immediately after waking up (for patients producing specimen at home)

Sputum labelling

Correct labelling is essential and will save time and prevent errors.

Label the container first, very clearly with:

- Name of clinic/hospital
- Name of patient and clinic/hospital number
- Date the specimen and indicate whether the specimen is spot or early morning
- Write clear instructions regarding what investigations are required on sputum request form
- Ensure all information on the container matches the one on the request forms to avoid rejection of specimen by the lab

Labelling should always be done on the body of the container as the lids could get mixed up during specimen processing.

Sputum storage

- Place the sputum bottle in a plastic bag, if possible, to prevent contamination
- Store sputum specimen in a fridge or cool shaded place if transport is not available immediately. Do not store in a freezer
- Send sputum specimens to the laboratory as soon as possible and do not store for more than a week before transportation
- Record the date on which the specimen was sent to the laboratory in the presumptive TB Register

Transportation of sputum specimens

- Transport specimens from rural health facilities to laboratories at least once per week
- Organize a sputum collection schedule for all facilities in the district
- Transport specimens to the laboratory in cool sputum transport boxes as high temperatures during transit will kill bacilli
- Protect specimens from direct sunlight during transportation
- Inform driver the reasons for transporting specimens, thereby ensuring that specimens go directly to the laboratory

Every working day, a responsible person should check the presumptive TB register to see which results are pending and then contact the laboratory to determine result status.

Close cooperation with the laboratory will produce quick results, resulting in starting bacteriologically proven patients on the correct treatment as soon as possible

Smear Microscopy

GeneXpert is the recommended initial diagnostic test while smear microscopy is used for monitoring TB patients' response to treatment. Demonstration of micro-organisms (commonly referred to as acid-fast bacilli or AFB) in the sputum sample using AFB microscopy method proves that the individual has smear-positive tuberculosis. The number of bacilli (AFB) seen in a smear reflects the patient's infectivity and severity of disease.

The laboratory will record the number of bacilli seen on each smear as in table below:

Table 6: Guide for grading results of smear microscopy (The Union)

Number of bacilli seen on a smear			Fields to examine	Results reported
No	AFB	per 100 oil immersion fields	At least 100	0
1-9	AFB	per 100 oil immersion fields	100	Scanty, indicate number (1-9)
10-99	AFB	per 100 oil immersion fields	100	+
1-10	AFB	per 1 oil immersion field	50	++
>10	AFB	per 1 oil immersion field	20	+++

All positive sputum results should be recorded in both the Laboratory and TB District registers in **red** ink for ease of identification. The laboratory identification number and the date the

examination was performed should be entered in the column next to that for the result of the examination.

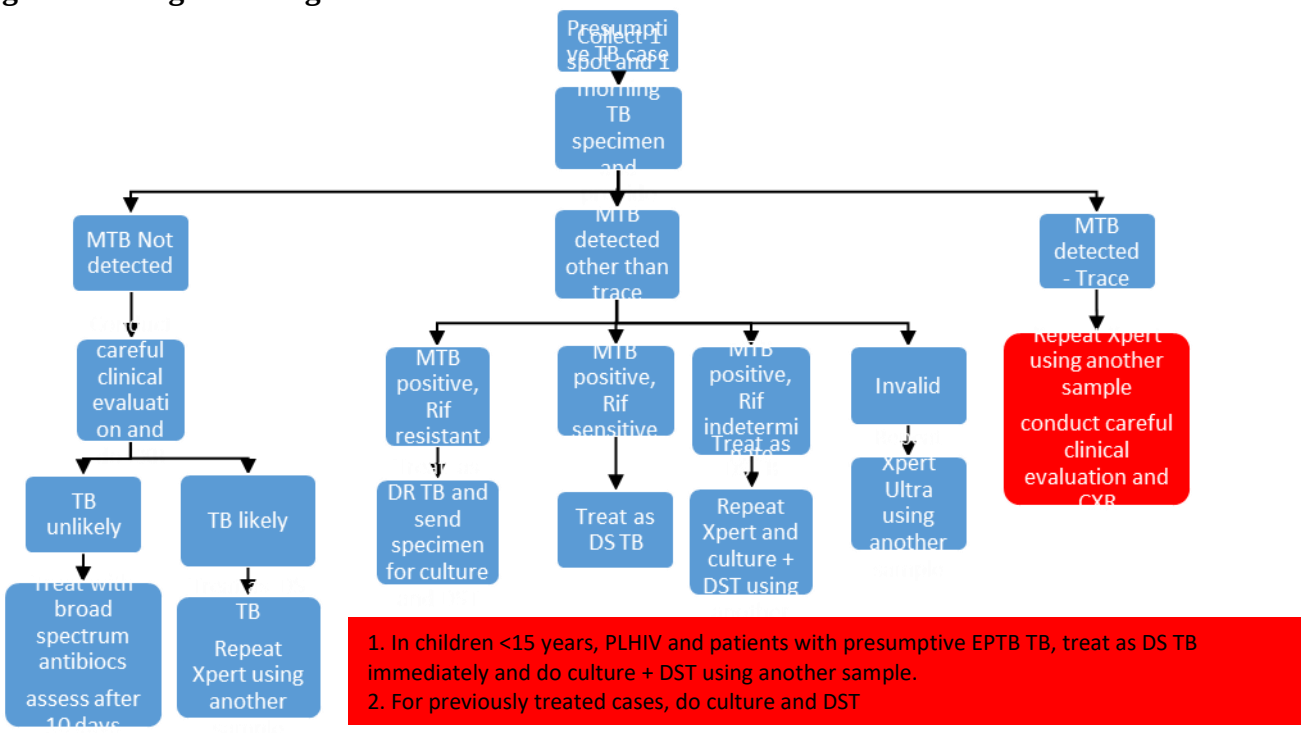
GeneXpert Ultra

This newer generation GeneXpert test is the recommended initial diagnostic test in Lesotho in line with WHO recommendation. The development of GeneXpert or Xpert MTB/RIF, a nucleic acid amplification test improved the diagnosis of TB and rifampicin resistance as this test had better sensitivity in comparison to AFB microscopy and provided results for rifampicin resistance at the same time. However, the sensitivity was still inadequate in patients with smear negative and HIV associated TB disease. Xpert MTB/RIF Ultra currently in use in Lesotho was developed to overcome this limitation.

Xpert Ultra is of particular value in diagnosis of TB disease in HIV-infected patients and children and in analysing extra pulmonary TB specimen such as CSF, lymph nodes and tissue specimen from patients who may not provide a sputum based specimen. Such patients also tend to have paucibacilliary disease. It is now also possible to analyse other types of specimen such as urine, stool, pleural and other effusions and pus with Xpert Ultra.

The sensitivity of Xpert MTB/RIF Ultra is 5% higher compared to older generation Xpert MTB/RIF assay although it has a 3.2% lower specificity. It is however, unlikely that the lowered specificity will result in significantly higher overtreatment in PLHIV, children and patients suspected to have EPTB.

Figure 2 – Diagnostic Algorithm



Line Probe Assays (LPA)

LPA is another molecular test available in Lesotho. Unlike GeneXpert Ultra, it is not an automated test, and it requires specialized laboratory facilities and trained personnel for proper interpretation. LPA is not recommended for diagnosis of TB, but it can be used for rapid diagnosis of drug resistance to both rifampicin and isoniazid as well as second line DST.

Culture and Drug Susceptibility Testing (DST)

Culture remains the gold standard for diagnosing TB. However, it is an expensive and slow diagnostic technique that takes up to 6 - 8 weeks to provide a definitive result. Culture results may therefore not be helpful in making a rapid individual diagnosis. Given the cost and long turnaround time, it is not routinely used under programme conditions. However, it remains an important tool in confirmation of treatment failure, diagnosis of EPTB, distinction between *M. tuberculosis* and NTM, and monitoring of DR-TB treatment.

DST is used to determine if an isolate is resistant to TB medications by evaluating growth in the presence of the drug (phenotypic) testing. Currently in Lesotho, there are two types of DST methods, namely molecular (GeneXpert and LPA) and phenotypic testing.

The accuracy of the testing varies by drug and is very reliable for rifampicin and isoniazid but less so for pyrazinamide and ethambutol. DST for second-line medications is reliable for the aminoglycosides, polypeptides and fluoroquinolones. It is less reliable for PAS, ethionamide and cycloserine.

Indications for sputum culture and DST:

High risk of MDR-TB as in:

- RIF resistant on GeneXpert testing
- Contacts of known MDR-TB cases with active TB
- Treatment failure patients
- History of multiple previous treatments in public or private sector

A standardized drug-resistant treatment regimen should be used as empiric treatment while awaiting DST results in all high risk patients.

Moderate risk of MDR-TB includes:

- Lost to follow-up or relapse patients
- Previous treatment for TB
- Migrant workers with new TB
- Health workers with new TB

Chest X-rays (CXR)

Chest radiography is not a substitute for bacteriologic examination and should only be considered after negative Xpert Ultra results. In this situation, a good quality CXR in combination with other clinical evidence provides support for diagnosing PTB.

One-third to half of PTB patients lack the classic radiographic findings.

In PLHIV, tuberculosis may present with atypical CXR findings and up to 5% may have normal chest radiography. Also, HIV-infection is known to be associated with CXR abnormalities even without tuberculosis. Despite these limitations, CXR may shorten delays in TB diagnosis in PLHIV and should be performed early in the course of investigation of presumptive tuberculosis. It is also an important entry point to diagnosing non-tubercular chest diseases, which are common among people living with HIV.

The presence of miliary shadows, unilateral pleural effusion and/or cavitation can be considered typical of TB and such cases should be initiated on appropriate treatment without delay.

Considerations for CXR

When TB is bacteriologically confirmed:

- Suspected complications, e.g. a breathless patient needing specific treatment (pneumothorax or pleural effusion)
- Help in diagnosing other lung diseases

When TB is *not* bacteriologically confirmed:

- If TB is clinically suspected despite negative investigations, the patient should have a CXR to help make a decision regarding diagnosis and treatment.

Radiographic Abnormalities Seen in PTB:

- No CXR pattern is absolutely diagnostic of PTB and immune status will generally influence the radiological findings (see table 1 below).

Table 1: CXR patterns in PTB based on immune status

Classical Pattern (immune-competent)	Immune-suppressed Pattern
Upper lobe infiltrates	Interstitial infiltrates (especially lower zones)
Bilateral infiltrates	Intrathoracic lymphadenopathy
Cavitation	No cavitation
Pulmonary fibrosis and shrinkage	No abnormalities

Diagnosis of Extra pulmonary TB

Introduction

Extra-pulmonary TB (EPTB) refers to a case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges, etc. For HIV patients, EPTB is a WHO stage 4 condition. Diagnosis should be based on at least one specimen with confirmed *M. tuberculosis* or histological or strong clinical evidence consistent with active EPTB. The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease. Involvement of lungs qualifies disease to be classified as PTB

Globally, EPTB accounts for 15% of new TB cases. However, EPTB is more commonly seen in children and in HIV-associated TB. The most common forms of EPTB include lymph node (especially in the neck or axilla), pleural (usually one-sided pleural effusion) and disseminated TB (disease that is not limited to one site in the body). Pericardial TB and TB meningitis are less frequent forms of EPTB but with serious consequences. Disseminated TB should be included in the differential diagnosis of any HIV-infected person presenting with rapid or marked weight loss, fever, and night sweats.

In general, clinical presentation of EPTB depends on the organ involved. Both pulmonary and extra-pulmonary disease is found in up to 50% of patients with HIV-related TB.

Box 1: Suggested clinical characteristics to assist the diagnosis of EPTB

Suggested clinical characteristics to assist the diagnosis of EPTB

Suspect EPTB in patients with:

- Unintentional weight loss with night sweats and temperature > 37.5 °C or feels feverish
- Breathlessness (effusion/pericarditis)
- Enlarged glands in neck/armpit
- Chest X-ray
    - Large heart (especially if symmetrical and rounded)
    - Pleural effusion
    - Enlarged lymph nodes inside the chest
- Chronic headache or altered mental state

Look and listen for:

- Swollen lymph nodes in the neck or armpits: ***Possible TB adenitis***
    - If present with other types of EPTB, it may provide the only way to confirm the diagnosis
- Signs of fluid in the chest: ***Possible TB pleural effusion***
    - Absent breath sounds
    - Reduced chest wall movement
    - Dull to percussion
- Signs of fluid around the heart: ***Possible TB pericarditis***
    - Heart sounds distant
    - Swollen legs and/or abdomen
    - Neck and hand veins distended with arm held above the shoulder
- Signs of meningitis: ***Possible TB meningitis***
    - Neck stiffness
    - Confusion
    - Abnormal eye movements

Generally, there is a significant delay in the diagnosis of EPTB. This can be partly attributed to vague symptoms of EPTB that overlap with other common diseases, absence of the classic systemic symptoms of TB in most cases, and shortage of diagnostic options. The clinician is advised to have high index of suspicion for EPTB and start treatment for TB based on clinical evidence (if bacteriologic or other evidences are lacking).

Clinical features and diagnosis of common EPTB forms

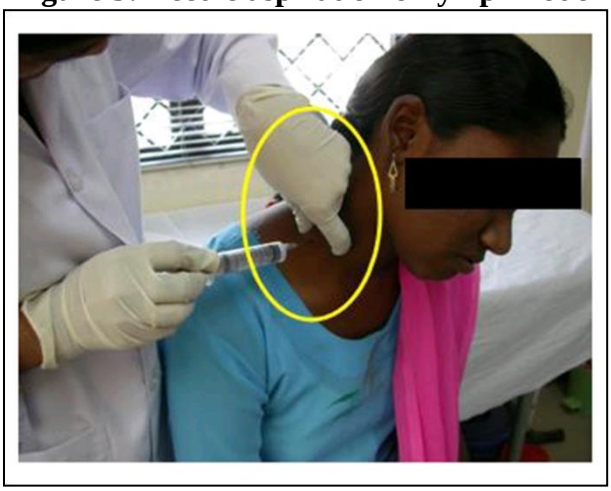
TB Lymphadenitis

TB of lymph nodes usually presents as a painless, firm, more than 2 cm in diameter, unilateral cervical lymph node enlargement. Over the subsequent months, the node could become fluctuant and might start to ooze pus (draining sinus). Other systemic symptoms are usually absent. Involvement outside of the cervical region is usually associated with systemic symptoms and tends to be a more severe illness.

In advanced HIV infection, the lymphadenopathy tends to be multifocal and is associated with major systemic symptoms like fever and weight loss. Also, disseminated disease is more common. Other sites of lymphadenopathy due to TB include intra-thoracic and intra-abdominal (mesenteric) which tend to be more common in children and HIV-infected individuals.

Other causes of similar lymph node enlargement include reactive lymphadenopathy, HIV-related lymphadenopathy, other bacterial infection and malignancies. Therefore, needle aspiration of the lymph node is recommended in the first visit of the patient.

Figure 3: Needle aspiration of lymph node



Needle aspiration and cytology/GeneXpert have a high diagnostic yield of up to 85% if done appropriately. If there is a discharge, GeneXpert of the fluid may suffice to confirm the diagnosis.

In every patient suspected of TB adenitis, lymph node aspiration should be performed and sent to the lab for diagnosis. If diagnosis is not confirmed by aspiration, excision biopsy can be considered.

The patient should be started on TB treatment immediately if:

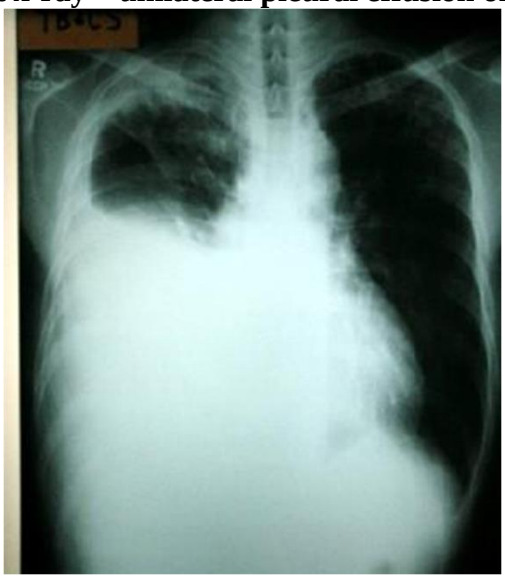
- The patient is HIV-infected and has features of disseminated TB (multiple sites of suspected TB, significant weight loss, and rapid clinical deterioration)
- TB adenitis is considered the most likely diagnosis and further investigations like excisional biopsy cannot be done due to economic and logistic issues

Pleural Effusion

Tuberculosis pleural effusion is one of the most common forms of EPTB. It is the most common form of HIV-related EPTB in adults and is associated with high mortality in the first two months of TB treatment.

The typical manifestation is acute onset of fever, pleuritic chest pain and cough. Sometimes it presents with an insidious onset of fever, malaise and weight loss. It usually presents with unilateral effusion, and if the effusion is massive, patients might present with shortness of breath. Chest X-ray typically shows unilateral pleural effusion mostly on the right side. Bilateral pleural effusion occurs in about 10% of cases.

Figure 3: Chest x-ray – unilateral pleural effusion on the right lung



Pleural tap should be done in all patients with the above presentation. The pleural fluid needs to be sent to the laboratory for biochemistry, cytology and bacteriological investigation (GeneXpert and culture).

Characteristics of pleural fluid analysis include:

- Straw coloured fluid

- Protein level is more than 2.5gm/l (exudative)
- Moderate number of white blood cells (usually between 500-2500/mm3) with more than 90% lymphocytes
- Adenosine deaminase (ADA) levels >100IU/L
- GeneXpert Ultra in pleural fluid testing has low sensitivity (50.9%) compared to culture which is positive in up to 30% of cases

TB Meningitis

TB meningitis classically starts with an initial 2-3 weeks of nonspecific symptoms of intermittent headache, malaise, low grade fever, followed by protracted headache, vomiting, confusion, neck stiffness and focal neurologic deficits. The clinical presentation has a wide spectrum ranging from chronic headache with minimal neurologic deficit to severe meningitis progressing to coma. In 75% of cases, concomitant involvement of other organs (especially lungs) is evident. As with miliary TB, TB meningitis is associated with high morbidity and mortality. A high index of suspicion and expedited diagnosis is necessary to ensure prompt initiation of life-saving treatment. Patients presenting with the above symptoms should be immediately referred to the hospital for diagnostic lumbar puncture. **Treat all cases of TB meningitis with 12 months of therapy.**

Cerebrospinal fluid analysis is very crucial in the diagnosis of TB meningitis.

- White blood cell count can be as high as 1500/mm3, predominantly lymphocytes. But, early in the disease polymorphonuclear leuckocytes might predominate.
- Protein level is moderately elevated (100-500 mg/dL).
- Glucose level is low (< 45 mg/dL).
- CSF should be sent for GeneXpert and culture.
- As most of the patients have concomitant involvement of the lungs, CXR should be done to all patients suspected of TB meningitis.

The prognosis of the patient relies mostly on age, duration of symptoms, and clinical stage of disease. Patients younger than 5 years or older than 50 years and those that have been sick for more than two months before treatment have a higher risk of death. Almost half of the patients with coma at presentation die or develop severe neurologic complications.

TB of Bones/Joints

TB of bones/joints can be divided in two major groups: Spinal TB (tuberculous spondylitis) and Joint TB (peripheral osteoarticular TB).

Spinal TB (Tuberculous spondylitis)

Spinal TB, also known as Pott's Disease, is the most common form of TB affecting bones and joints. Thoracic vertebrae are more commonly affected than lumbar vertebrae with less common involvement of cervical or sacral vertebrae. Spinal TB usually occurs in children and young adults. Initial symptoms are usually back pain with stiffness of the muscles around the vertebrae.

Other systemic symptoms are rarely seen and evidence of other organ involvement is usually absent. Since the symptoms are vague and other TB symptoms are not seen, diagnosis of spinal TB is usually delayed until an advanced stage where patients develop deformity, paralysis and sometimes even sinus formation. In the initial phase vertebral X-rays are usually normal. As the disease progresses, anterior wedge shaped destruction of adjacent vertebrae with destruction of the intervertebral disc and narrowing of the intervertebral space is evident (Fig 5). High index of suspicion, prompt diagnosis and initiation of treatment are crucial to prevent permanent disability. Clinicians should include spinal TB in the differential diagnosis when patients present with severe back pain and evidence of collapsed vertebrae. In some severe cases, surgical interventions might be needed. **Treat all cases of spinal TB with 12 months of therapy.**

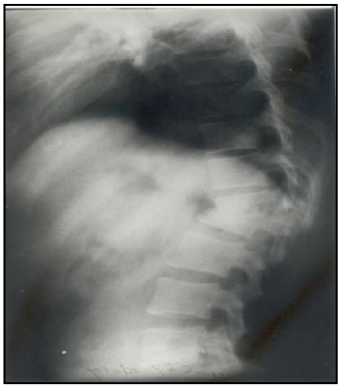


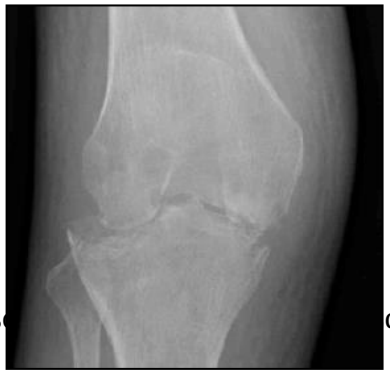
Figure 5: Lateral X-ray of the thoracolumbar vertebrae

Wedge shaped (arrow) collapse of Lumbar 1 and 2 vertebrae suggestive of spinal TB.

Joint TB (Osteoarticular TB)

TB of joints is a slowly progressive disease that occurs mainly in the large joints of the hip and knee, but TB of smaller joints and multiple joint involvements can also occur. Patients often report a history of trauma as an initial insult which is followed by a chronic dull ache in the specific joint for weeks to months. Patients also notice progressive swelling of the joint. Typical features of acute inflammation might be absent. In chronic cases, cold abscesses and pus discharge can develop. Systemic symptoms are not seen often. Early in the course of the illness x-rays of the affected joint is normal or might reveal soft tissue swelling alone. Later in the course of illness, decreased bone density, peri-articular bone destruction, and periosteal thickening can be seen.

Figure 6: X-ray of the right knee



Destruction of the articular area of the tibia and femur with joint space narrowing suggestive of TB.

TB Pericarditis

TB pericarditis can present acutely with fever, cough, severe shortness of breath, low blood pressure for few days, or insidiously as milder and progressive heart failure. On examination, patients with TB pericarditis will have diminished heart sounds. Up to 40% of cases present also with pleural effusion.

In patients suspected of TB pericarditis, obtain a CXR. On CXR, the heart shadow is enlarged and boot shaped. When pleural effusion is identified, it should be tapped and analysed. Patients must be admitted for close monitoring and placed on bed rest. Blood pressure, respiratory and pulse rate should be monitored regularly. Heart failure should be controlled with appropriate medications. TB treatment should be started promptly and adjunct steroid therapy.

Abdominal TB

TB may affect different parts of the gastrointestinal tract down to the rectum and anus. Abdominal TB may be acute or chronic, and patients often present with fever, weight loss, abdominal pains, and distension with diarrhea or constipation. Abdominal TB accounts for about 3% of all the cases of TB, and 12% of the EPTB cases. Diagnosis is often difficult due to nonspecific symptoms, but histopathology examination of specimen collected from affected area can assist with diagnosis.

Table 2: Summary of Investigations for EPTB

Anatomical site	Recommended investigations
TB adenitis (especially from cervical region)	• Fine needle aspiration (FNA) for GeneXpert and cytology • Sputum if coughing for GeneXpert • Lymph node biopsy for histology and GeneXpert
Miliary TB	• Sputum if coughing for GeneXpert • CXR • TB Blood culture • Perform additional diagnostic tests as appropriate for associated symptoms and signs e.g Lumbar puncture for GeneXpert if TB meningitis suspected.
TB meningitis	• Lumbar puncture (LP) for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), Culture and DST • Sputum for GeneXpert • CXR
Pleural effusion	• CXR • Pleural tap for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), Culture and DST • Sputum for GeneXpert • Pleural biopsy for histology

Abdominal TB	• Abdominal ultrasound for ascites, lymph nodes, hepatosplenomegaly • Ascitic tap for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose) Culture and DST • Sputum for GeneXpert • CXR
TB of spine/bones/joints (osteoarticular TB)	• Spinal X-ray, • Joint tap for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose) Culture and DST • Synovial biopsy for histology and GeneXpert • Sputum for GeneXpert
Pericardial TB	• CXR • ECHO (chest ultrasound) for pericardial thickening and effusion • Pericardial tap for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose) Culture and DST • Sputum for GeneXpert
Neonatal TB	• Chest x-ray, • Lumbar puncture for GeneXpert, WBC count and differential, biochemical analysis (protein and glucose), culture and DST • Gastric aspirates for GeneXpert • Histopathology examination of the placenta for AFB and granulomata. • Neonatal abdominal ultrasound for portal lymphadenopathy and primary liver focus • Evaluation of mother for tuberculosis.
Drug resistant TB – any anatomical site	• Culture and DST of relevant specimens
Renal TB	• Early morning urine for GeneXpert, culture and DST • Ultrasound • Urinalysis

Treatment of Tuberculosis

The Basics of Treatment

The key to stopping the spread of TB is early detection and effective treatment of persons who are coughing up (aerosolizing) living TB bacilli. For treatment to be effective, it is necessary that correct medications are given at the right doses for the appropriate duration.

The aims of TB treatment in Lesotho are the following:

- To cure the patient of active TB and restore quality of life and productivity
- To prevent death from TB or its complications
- To decrease transmission of the disease to others
- To prevent relapse of TB
- To prevent the development of drug resistance.

Essential TB Medications

There are three primary properties of TB medications: bactericidal, bacteriostatic (sterilizing activity) and ability to prevent resistance. For effective TB treatment, combinations of these properties are required in a treatment regimen. Individual TB medications possess these properties to different extents.

In a tuberculous lesion there are various populations of bacilli:

- Metabolically active
- Intermediately active
- Semi dormant bacilli (persisters), which undergo occasional spurts of metabolism.
- Dormant bacilli which may become active

Different TB medications act against the different populations of bacilli. Bacilli may occur extra-cellularly or intra-cellularly. The pH in the extracellular space is usually neutral or alkaline, whereas it is acidic intra-cellularly. Some TB medications perform the best in acidic environments, while others perform best in alkaline environments.

Table 10: Essential TB medicines

Medication	Mode of action	Recommended Daily Dose in Adults (mg/kg)	Recommended Daily Dose in Children (mg/kg)	Maximum Daily Dose
Isoniazid (H)	• Has early bactericidal activity • Active in both acid and alkaline media (but mainly alkaline); and against intra and extra cellular bacilli • Predominantly active against rapid and intermediate growing bacilli in cavities • Bactericidal with high potency, killing more than 90% of the total population of TB bacilli during the first few days of treatment • Inhibits cell wall synthesis	5 (4-6)	10 (7-15)	300 mg
Rifampicin (R)	• Has rapid onset sterilizing action • Active in both alkaline and acid media; intra and extra cellular bacilli • Active against all bacterial populations including dormant populations • High potency • Most effective sterilizing drug • Inhibits mRNA synthesis	10 (8-12)	15 (10-20)	600 mg
Pyrazinamide (Z)	• Most active drug against bacteria in intracellular space (within macrophages) and extracellular acidic space • Mainly active against persistent bacilli than actively replicating organisms • Bactericidal with low potency but good sterilization activity • Disrupts cytoplasmic membrane function	25 (20-30)	35 (30-40)	
Ethambutol (E)	• Active in both alkaline and acid media • Active against dividing organisms but less so against slow growers • Bacteriostatic with a low potency • Minimises the emergence of drug resistance • Disrupts synthesis of cell wall	15 (15-20)	20 (15-25)	

Recommended Standard Treatment Regimens for Adults

Treatment of all forms of TB in Lesotho is based on the WHO-recommended treatment regimens for the appropriate case definitions. Through the assistance of the Global TB Drug Facility (GDF), Fixed-Dose Combinations (FDCs) are used in the National TB Programme for both adults and children.

Treatment of New Tuberculosis Cases

In these guidelines we have adopted the use RHE in the continuation phase in line with WHO recommendation for settings with high INH mono-resistance. All new TB cases shall be treated according to the treatment regimen for a New TB Case which involves administration of RHZE in the first 2 months of the initial phase and RHE in the 4 months of continuation phase. The recommended treatment regimen for new cases is represented as 2HRZE/4HRE. Patients should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy. Table 3 below shows recommended Lesotho regimen and doses that all treating clinicians are to adhere to.

Table 3: Recommended treatment regimen and dosages for new adult TB cases

Phase of treatment	Drugs	Weight in kg			
		30-39	40-54	55-70	>70
Intensive phase of 2 months	**(RHZE)*** (150mg/75mg/400mg/275mg)	2 tabs daily	3 tabs daily	4 tabs daily	5 tabs daily
Continuation phase of 4 months	**(RHE) (**150mg/75mg/275mg)	2 tabs daily	3 tabs daily	4 tabs daily	5 tabs daily

*****Fixed-dose combination (FDC) drugs

Previously treated patients

Previously treated TB patients require further investigations to determine optimal course of therapy. Previous TB treatment is a strong determinant of drug resistance, and this should be investigated since drug resistance hinders the effectiveness of first-line TB medications and amplifies resistance.

All previously treated TB patients should provide specimen for culture and drug susceptibility testing (DST) at or before start of treatment. Rapid molecular testing (GeneXpert, LPA) should also be performed in all previously treated cases. If rapid testing reveals rifampicin resistance, the patient should receive empiric DR treatment while awaiting phenotypic DST results. Those patients with results showing rifampicin sensitivity, should be treated with first line regimen.
Retreatment regimen is no longer recommended for patients who require retreatment for TB

Treatment regimens in special circumstances

Treatment for pregnant women

The benefit of treating active TB disease in a pregnant woman far outweighs the risks that the medications may pose to both the mother and the foetus. No changes to the regimen is necessary.

Treatment for breastfeeding women

A woman who is breastfeeding and has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby. ***All first-line TB medications are compatible with breastfeeding and a woman can safely continue to breastfeed her baby during treatment***. The child should continue to breastfeed normally but be given prophylactic isoniazid and rifampicin (RH) for 3 months. BCG vaccination of the newborn should be postponed until the end of RH prophylaxis.

Treatment for women taking the oral contraceptive pill

Rifampicin interacts with the contraceptive pill with a risk of decreased protective efficacy against pregnancy. A woman on oral contraceptives may choose between the following two options while receiving treatment with rifampicin: 1) take an oral contraceptive pill containing a higher dose of oestrogen *(50* mcg) or 2) switch to another form of contraception. This decision should be made after consultation with a physician.

Treatment for patients with liver disorders

Isoniazid, rifampicin and pyrazinamide are all associated with hepatitis. Of the three medications, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice; pyrazinamide is the most hepatotoxic. Patients with the following conditions can receive the usual short-course chemotherapy regimen provided that there is no clinical evidence of chronic liver disease: hepatitis virus carriage, a past history of acute hepatitis, excessive alcohol consumption. However, hepatotoxic reactions to TB medications may be more common in these patients and should be anticipated.

Patients with liver disease should not receive pyrazinamide. Isoniazid plus rifampicin plus one or two non-hepatoxic drugs such as streptomycin and ethambutol can be used for the total duration of 8 months. Alternative regimens are 9 RE or 9 SHE in the initial phase followed by HE in the continuation phase, with a total treatment duration of 12 months. Therefore, recommended regimens are 2 SHRE/ 6HR *or* 9RE *or* 2 SHE / 10HE.

In case of acute hepatitis, which may or may not be related to TB or TB treatment, the medical officer's clinical judgment is required. In some cases, TB treatment may be deferred until acute hepatitis has resolved. When the clinician decides to treat TB during acute hepatitis, the combination of SE for 3 months is the safest option. If the hepatitis has resolved, the patient can receive a continuation phase of 6 months of RH. If the hepatitis fails to resolve, SE should be continued for a total of 12 months.

Expert consultation is advised in treating patients with advanced or unstable liver disease in conjunction with clinical and laboratory monitoring.

Treatment of patients with renal failure

Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. Patients with renal failure can take normal dosages. Ethambutol is excreted by the kidney. Because of increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. Where facilities can monitor renal function closely, it may be possible to give ethambutol in reduced doses or given intermittently. The safest regimen to administer to patients with renal failure is 2 HRZE/ 4 HRE.

All patients that fall under the category "special circumstances" should be referred to and managed by an experienced Medical Officer.

The Role of Adjuvant Steroid Treatment

Adjuvant steroid treatment is recommended in the management of TB meningitis and pericarditis where it may decrease morbidity and mortality. Steroids may also be used as outlined below.

Adjuvant steroid therapy is recommended in the following conditions:

- TB meningitis (decreased consciousness, neurological defects, or spinal block).
- TB pericarditis (with effusion or constriction).

Other uses

- TB pleural effusion (when large with severe symptoms).
- Hypoadrenalism (TB of adrenal glands).
- TB laryngitis (with life-threatening airway obstruction).
- Severe hypersensitivity reactions to TB medications.
- Renal tract TB (to prevent ureteric scarring).
- Massive lymph node enlargement with pressure effects.
- IRIS (with clinical manifestations listed above)

The suggested treatment doses of prednisolone are as follows: prednisolone 1-2 mg/kg given once daily (max 80mg) tapered over 6 -8 weeks in TB meningitis. Duration of steroid use will depend upon the clinical details and should be evaluated on a case-by-case basis. However, use for longer than 10 days will require a gradual decrease over several weeks.

Steroids are immuno-suppressants which may increase the risk of opportunistic infections in HIV-infected patients. However, TB/HIV patients are still likely to benefit from the use of steroids in the presence of the above conditions.

Table 4: Recommended doses of adjuvant steroid Therapy

Indication	Prednisolone Treatment
TB Meningitis	1 -2mg/kg, max 80 mg/d for 4 weeks then taper off over 6 -8 several weeks
TB Pericarditis	1 -2mg/kg max 80 mg/d for 4 weeks, then 40 mg/d for 4 weeks then taper off over several weeks

Monitoring TB Patients during Treatment

Overview

Monitoring treatment is critical to TB control. It enables the clinician and the National TB program to:

- Monitor and record the response to treatment, and decide on actions to take in response to monitoring results;
- Detect and manage drug-induced toxicity;
- Encourage adherence and manage treatment interruption;
- Use cohort analysis to evaluate treatment outcomes.

Table 4: Monitoring the patient

Visit	Patient Monitoring	Other
Treatment initiation	Patient preparation; Identification of treatment supporter*	Evaluation of household contacts
2 weeks	Symptom evaluation, weight, adherence, tolerance, side effects; Education of treatment supporter	Evaluation of household contacts
4 weeks	Symptom evaluation, weight, adherence, tolerance, side effects	
6 weeks	Symptom evaluation, weight, adherence, tolerance, side effects	Give bottles to collect sputum at end of intensive phase
2 months	Symptom evaluation, weight, adherence, tolerance, side effects; sputum smear for all patients with pulmonary TB	
3 months	Symptom evaluation, weight, adherence, tolerance, side effects	
4 months	Symptom evaluation, weight, adherence, tolerance, side effects	Give bottles to collect sputum at month 5
5 months	Symptom evaluation, weight, adherence, tolerance, side effects; sputum smear for all patients with pulmonary TB	Give bottles to collect sputum at end of treatment
6 months	Symptom evaluation, weight, adherence, tolerance, side effects; sputum smear for all patients with pulmonary TB	

* Treatment supporter should report to health facility for education regarding TB and DOT monitoring within the first week of TB treatment.

All patients, their treatment supporters and health workers should be instructed to report the persistence or reappearance of TB symptoms (including weight loss), symptoms of adverse drug reactions, or treatment interruptions.

- Patient weight monitoring is key. Adjust dosages based on weight changes.
- Additional monitoring and trigger actions are discussed below.
- All TB medications should be recorded on the treatment card and the bacteriological responses at 2 months (+/- 3 months), 5 months and end of treatment.
- Adverse reactions should be recorded for every patient on the TB Treatment Card in the notes section and appropriately documented in the patient's bukana.

Assessing treatment response in pulmonary TB patients

Response to treatment in patients with pulmonary TB, both new and previously treated, is monitored by sputum smear examination.

If a patient is found to have rifampicin resistant strain of TB at any time during treatment, that patient is referred to an MDR-TB treatment programme and their outcomes recorded under MDR TB.

Patients with rifampicin resistant TB include RR, MDR-TB and XDR-TB
Two sputum samples should be collected when the patient is given the last dose of the intensive phase treatment. Sputum specimens should be collected for smear examination at each follow-up sputum check. They should be collected without interrupting treatment and transported to the laboratory as soon as possible thereafter; if a delay is unavoidable, specimens should be kept in a cool shaded place for up to three days or refrigerated for longer duration.

Smear status at the end of the intensive phase is a poor predictor of which new patients will relapse. However, detection of a positive sputum smear remains important as a trigger for the patient assessment outlined below as well as for additional sputum monitoring.

The proportion of smear-positive patients with sputum smear conversion at the end of the intensive phase is also an indicator of TB programme performance.

A positive sputum smear at the end of the intensive phase may indicate any of the following:

- Initial phase of therapy was poorly supervised and patient adherence was poor;
- Poor quality of TB medications;
- Doses of TB medications are below the recommended range;
- Resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load;
- There are co-morbid conditions that interfere either with adherence or with response;
- The patient has drug-resistant *M. tuberculosis* that is not responding to first-line treatment;
- Non-viable bacteria remain visible by microscopy.
- Non-tuberculous Mycobacteria (NTM)

For patients who are smear positive at the end of the intensive phase:

- Carefully review clinical and social issues.
- Efforts should be made to strengthen adherence support,
- Explore and address any reasons for interruptions.
- Do molecular DST (GeneXpert) to rule out DR

New Pulmonary TB Patients

Additional monitoring is needed for new patients whose sputum smear is positive at the end of the intensive phase. For those patients, sputum should be sent for culture and drug susceptibility testing (DST). However, the patient will start continuation phase while awaiting results.

Treatment modifications will only be made based on culture/DST results. Rapid DST using Xpert Ultra is recommended.

Patients will also have sputum smear analysis at fifth and final months of treatment. If either is positive, the patient has failed treatment, and treatment is stopped. Sputum should be sent for rapid molecular testing Genexpert and LPA, culture, and DST with treatment restarted based on results. For patients at high-risk of MDR-TB, empiric drug-resistant regimen is initiated with treatment modified based on DST results. Patients not at high-risk for MDR-TB and those with drug-sensitive LPA results should be restarted on New TB Treatment regimen.

Be careful when defining failure on the basis of microscopy alone; a positive smear might be due to presence of dead bacilli, especially in patients who started treatment with a high bacilli load.

Always try to confirm the failure:

- By culture and DST (Molecular and phenotypic)
- By clinical evaluation of the patient (clinical evaluation can be sufficient if culture is not available immediately)

Poor response to treatment always necessitates further investigation and intervention.

5.2.2 New bacteriological negative PTB

Most patients with bacteriologically-negative PTB at the start of treatment will remain smear-negative throughout treatment. However, it is possible for a patient who was smear-negative to become smear positive by month 2, and this may represent disease progression. Send two sputum samples at the end of month 2. If both smears are negative no further sputum should be sent. If one smear is positive send a sputum specimen for GeneXpert, LPA, culture and DST, and proceed to the continuation phase. Further monitoring is the same as for new bacteriologically confirmed PTB patients above.

Role of Chest X-Ray in Monitoring

Chest radiography is not needed for routine monitoring of pulmonary TB and should not be used to determine if treatment is successful. Chest x-ray may be needed for clinical indications – patient deterioration, co-morbid conditions, or suspected complications.

Extra-Pulmonary TB

For patients with extra-pulmonary TB, clinical monitoring, including weight gain, is the primary method of assessing the response to treatment.

Recording Standardized Treatment Outcomes

At the end of the treatment course for each individual patient, the District TB Coordinator/Officer records the treatment outcome in the District TB Register. The sputum smear performed at the end of treatment helps to establish the final outcome of treatment.

Cohort Analysis of Treatment Outcomes

A cohort is a group of patients diagnosed and registered for treatment during a specific time period (usually one-quarter of a year). Evaluation of treatment outcome in new bacteriologically-proven patients is used as a major indicator of programme quality. Outcomes in other patients (previously treated, pulmonary clinically diagnosed, extra-pulmonary) are analyzed in separate cohorts.

Cohort analysis is the key management tool used to evaluate the effectiveness of the national TB control programme. It enables the identification of problems, so that the programme managers and staff can institute appropriate action to overcome them and improve programme performance. Evaluation of the outcomes of treatment and trends must be done at peripheral, district, regional and national levels to allow any necessary corrective action to be taken. It can also identify districts or units that are performing well and allows for positive feedback to be provided to staff; successful practices can then be replicated elsewhere.

The district TB coordinator/ local TB officer should perform cohort analysis of treatment outcomes every quarter-year and at the end of every year. A typical cohort consists of all TB patients registered during a quarter. New patients and subcategories of previously treated patients (relapses, return after loss-to-follow-up, failures) should be analyzed as separate cohorts because they have different characteristics and expected results.

Evaluation of outcome at the end of treatment should be undertaken as soon as possible after the last patient in the cohort completes treatment.

Outcomes are routinely evaluated at the beginning of the quarter following the completion of treatment by the last patient in that cohort. This information is transmitted in quarterly reports. After local review, district reports on treatment outcome are forwarded to the NTLP each quarter. The NTLP M & E verifies that district reports are correct, complete and consistent; compile cohort analysis reports on the bacteriologically-proven patients in the district; and submit the report to the HMIS. The NTP compiles cohort analysis reports on bacteriologically-confirmed TB patients registered nationally, evaluates, and provides feedback to the programme staff through biannual reviews.

Management of Treatment Interruption

If a patient misses an arranged appointment to receive treatment, the patient should be contacted (through existing retention strategies) within 2 days after missing appointment during the initial phase, and within a week during the continuation phase. It is important to find out the cause of the patient's absence so that appropriate action can be taken and treatment can continue.

Contact patients within two days of missing appointment during intensive phase and within 7 days during continuation phase

The management of patients who have interrupted treatment takes into consideration several factors, each of which, if present, will necessitate further caution and additional interventions:

- Interruption occurs in the intensive, rather than the continuation, phase
- Interruption occurs early (rather than later) in the continuation phase
- The interruption is of long duration
- The patient is immuno-compromised (living with HIV or another condition)
- The patient had poor response to treatment before the interruption
- The patient is found to be smear or culture-positive upon return from loss to follow-up
- Drug-resistant disease is known or presumed

Table 6: Management of TB treatment interruption

<table>
<tr><td colspan="4">Interruption for less than 1 month
• Trace patient
• Address the cause of interruption
• Continue treatment and prolong it to compensate for missed doses</td></tr>
<tr><td colspan="4">Interruption for 1-2 months
Action 1 Action 2</td></tr>
<tr><td rowspan="3">• Trace patient
• Address the cause of the interruption
• Do 2 sputum smears. Continue treatment while waiting for results.</td><td>If smears negative or EPTB</td><td colspan="2">Continue treatment and prolong it to compensate for missed doses</td></tr>
<tr><td rowspan="2">If one or more smears positive</td><td>Treatment received:
< 5 months</td><td>Continue treatment and prolong it to compensate for missed doses</td></tr>
<tr><td>Treatment received:
> 5 months</td><td>LPA and treat based on results</td></tr>
<tr><td colspan="4">Interruption for 2 months or more (lost-to-follow-up)</td></tr>
<tr><td rowspan="2">• Do 2 sputum smears
• Address the cause of the interruption, if possible
• No treatment while waiting for results</td><td>If smears negative or EPTB</td><td colspan="2">Clinical decision on individual basis whether to restart or continue treatment, or no further treatment</td></tr>
<tr><td>If one or more smears positive</td><td>LPA (moderate risk of RR TB) New TB Case Treatment regimen</td><td>LPA, Rifampicin sensitive Previously treated TB case Treat with FL regimen

RR,
(high MDR-TB risk). Treat with MDR TB regimen</td></tr>
</table>

Prevention of INH-Induced Peripheral Neuropathy

Health personnel can prevent some drug-induced side-effects, for example isoniazid-induced peripheral neuropathy. This usually presents as numbness or a tingling or burning sensation of the hands or feet and occurs more commonly in pregnant women and in people with the following conditions: HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease, renal failure. All patients should receive preventive treatment with pyridoxine 25 mg/day along with their TB treatment.

Monitoring and recording adverse effects

Most TB patients complete their treatment without any significant adverse drug effects. However, a few patients do experience adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary.

Health personnel can monitor adverse drug effects by teaching patients how to recognize the symptoms of common effects, urging them to report if they develop such symptoms, and by asking about symptoms when patients come to collect medication refills.

Adverse reactions to drugs should be recorded on the TB Treatment Card under "Observations" and in the patient's bukana

Symptom-Based Approach to Managing Side-Effects of TB Medications

The adverse effects of essential TB medications are described in Table 7 shows a symptom-based approach to the management of the most common adverse effects, which effects are classified as major or minor. In general, a patient who develops minor adverse effects should continue the TB treatment and be given symptomatic treatment. If a patient develops a major side-effect, the treatment or the responsible drug is stopped; the patient should be urgently referred to a clinician or health care facility for further assessment and treatment. Patients with major adverse reactions should be managed in a hospital.

Management of Cutaneous Reactions

If a patient develops itching without a rash and there is no other obvious cause, the recommended approach is to try symptomatic treatment with antihistamines and skin moisturizing, and continue TB treatment while observing the patient closely. If a skin rash develops, however, all anti-TB drugs must be stopped.

Once the reaction has resolved, anti-TB drugs are reintroduced one by one, starting with the drug least likely to be responsible for the reaction (rifampicin or isoniazid) at a small challenge dose, such as 50 mg isoniazid. The dose is gradually increased over 3 days. This procedure is repeated, adding in one drug at a time. A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction. The alternative regimens listed in section 1.10.2 below are also applicable when a particular drug cannot be used because it was implicated as the cause of a cutaneous reaction.

Table 7: Guide to performing anti-TB drug challenge and re-introduction

	Likelihood of causing a reaction	Challenge doses		
Drug		**Day 1**	**Day 2**	**Day 3**
Rifampicin	Least likely	75 mg	300 mg	Full dose
Isoniazid		50 mg	300 mg	300mg

Pyrazinamide		250 mg	1 gr	Full dose
Ethambutol		100 mg	500 mg	Full dose

Management of Drug-Induced Hepatitis

Of the first-line anti-TB drugs, isoniazid, pyrazinamide and rifampicin can all cause liver damage (drug-induced hepatitis). In addition, rifampicin can cause asymptomatic jaundice without evidence of hepatitis. It is important to try to rule out other possible causes before deciding that the hepatitis is induced by the TB regimen.

The management of hepatitis induced by TB treatment depends on:

- Whether the patient is in the intensive or continuation phase of TB treatment;
- The severity of the liver disease;
- The severity of the TB; and
- The capacity of the health unit to manage the side-effects of TB treatment.

If it is thought that the liver disease is caused by the anti-TB drugs, all drugs should be stopped. If the patient is severely ill with TB and it is considered unsafe to stop TB treatment, a non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started.

If TB treatment has been stopped, it is necessary to wait for liver function tests to revert to normal and clinical symptoms (nausea, abdominal pain) to resolve before reintroducing the anti-TB drugs. If it is not possible to perform liver function tests, it is advisable to wait an extra 2 weeks after resolution of jaundice and upper abdominal tenderness before restarting TB treatment.

If the signs and symptoms do not resolve and the liver disease is severe, the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started (or continued) for a total of 18–24 months.

Once drug-induced hepatitis has resolved, the drugs are reintroduced one at a time. If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. Some advise starting with rifampicin because it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective agent. After 3–7 days, isoniazid may be reintroduced. In patients who have experienced jaundice but tolerate the reintroduction of rifampicin and isoniazid, it is avoid pyrazinamide.

Alternative regimens depend on which drug is implicated as the cause of the hepatitis.

If rifampicin is implicated, a suggested regimen without rifampicin is 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol.

If isoniazid cannot be used, 6–9 months of rifampicin, pyrazinamide and ethambutol can be considered.

If pyrazinamide is discontinued before the patient has completed the intensive phase, the total duration of isoniazid and rifampicin therapy may be extended to 9 months. If neither isoniazid nor rifampicin can be used, the non-hepatotoxic regimen consisting of, ethambutol and a fluoroquinolone should be continued for a total of 18–24 months.

- *When hepatitis with jaundice occurs during the intensive phase* of TB treatment with isoniazid, rifampicin, pyrazinamide and ethambutol: once hepatitis has resolved, restart the same drugs EXCEPT replace pyrazinamide with streptomycin to complete the 2-month course of initial therapy, followed by rifampicin and isoniazid for the 6-month continuation phase.
- *When hepatitis with jaundice occurs during the continuation phase:* once hepatitis has resolved, restart isoniazid and rifampicin to complete the 4-month continuation phase of therapy.

Table 7: Symptom-based approach to managing side-effects of anti-TB drugs

Side-effects	Drug(s) probably responsible	Management
Major	*Stop responsible drug(s) and refer to clinician urgently*	
Skin rash with or without itching	isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin and refer to MDR TB centre
Minor	*Continue anti-TB drugs, check drug doses*	
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime.
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal

Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration

Chapter: TB/HIV Management

Background/Rationale for TB/HIV Integrated Services

TB and HIV are closely interrelated. TB is the most frequent cause of deaths worldwide, despite progress in access to ART. Thus, HIV is the single most important factor fueling the TB epidemic in settings with a high prevalence of HIV infection. Global data in 2016 indicated that PLHIV were 21 times more likely to develop active TB than those without HIV infection. For people living in the same country, the likelihood of TB in PLHIV increases to between 20 – 40 times compared to HIV-negative individuals.

This occurs basically through two mechanisms:

- Reactivation of latent TB infection to TB disease due to HIV-related immunodeficiency
- Rapid progression from recent TB infection (including TB re-infection) to TB disease

In Lesotho 70% of TB patients (2017) were co-infected with HIV according to programmatic monitoring.

Early diagnosis of TB in HIV-infected patients is critical to ensure early initiation of treatment, to minimize the negative effects of TB on HIV progression, and halt TB transmission in the community. Proper case management of TB can prolong the survival of PLHIV. Likewise, early diagnosis of HIV in TB patients will enable early initiation of HIV care and treatment, and this has been shown to reduce morbidity and mortality of TB/HIV co-infected patients.

TB/HIV Integration/Collaboration

Collaboration between TB/HIV services is crucial to address the impact from the two diseases. This should span all the key levels from the national program through the district health system and facilities to the communities.

This collaboration should embrace the following thematic areas:

- Establishing mechanisms for collaboration between HIV and TB services
- Reducing the burden of TB in PLHIV and
- Reducing the burden of HIV in TB patients

Establishing the Mechanism for TB/HIV Collaboration

For efficient coordination of TB/HIV activities the following areas continue to be addressed:

- Coordinating body at central level (TB/HIV Technical Advisory Committee), at district level (HIV/TB Coordination Meetings), at facility level (Multidisciplinary Teams) to manage TB/HIV services.
- Joint TB/HIV planning, joint resource mobilization (both financial and human), capacity development (including training), TB/HIV advocacy, communication and social mobilization (ACSM)

- Joint operational research activities to inform national policy and strategy development so as to improve service delivery.
- Joint monitoring & evaluation of collaborative TB/HIV activities. This ensures timely assessment of quality, effectiveness, coverage and delivery of collaborative TB/HIV activities.
- Joint enhancement of community involvement in collaborative TB/HIV activities through support groups for PLHIV, DOT supporters, and community-based organizations. Communities can also be mobilized to help implement collaborative TB/HIV activities.

Integration of TB and HIV services at the facility level is necessary for ensuring effective TB/HIV collaboration at this level.

Reducing the Burden of TB in PLHIV

Integration of services is essential for addressing this challenge. The following include the activities to be implemented:

- Intensified Case Finding (ICF) and prompt initiation of TB treatment
- TB Preventive Therapy (TPT) for Latent TB Infection
- Infection Control (IC) for TB in congregate settings

Integration of TB services in the HIV care and treatment settings is key for delivering the services. This will call for enhanced capacity of providers in HIV services to routinely screen for TB in all PLHIV attending HIV services and promptly provide TB treatment for identified cases. In settings where integration is not yet implemented, effective referral mechanisms must be established and maintained between the HIV and TB services so that patients are able to access the dual services without any hindrance. The above interventions must be implemented alongside the care services directed at HIV.

ICF

TB cases are routinely detected through passive case-finding, when symptomatic patients present to health services for diagnosis and treatment. Unfortunately, symptomatic patients often present multiple times before they are appropriately investigated for TB. Intensified case-finding for TB (ICF) differs from passive case-finding in that screening and the diagnostic work up for TB are initiated by the provider among PLHIV thus detecting TB earlier. This helps to reduce TB associated morbidity and mortality.

HIV- infected persons are at a higher risk of developing TB disease and may present with varied atypical features making the diagnosis difficult, thus the need to implement ICF. This should be done routinely at every clinical visit for all PLHIV using the nationally approved TB screening tool.

ICF is essential to exclude active TB, which requires treatment with a TB treatment regimen. TB screening should be routine in all the areas of the facility, especially targeting the following areas: Outpatients, HIV clinics, Maternal Child Health Clinics, and the wards. Diagnosis of TB should be seamlessly integrated into HIV care.

Begin diagnostic procedures in the HIV clinic for all patients with a positive TB screen (presumptive TB) by sending sputum or other specimen for appropriate laboratory investigations, referring for chest x-ray if indicated, and doing other investigations as indicated.

ICF should be intimately linked to prompt provision of TB treatment services, with comprehensive registration of all cases.

TPT

Tuberculosis remains the leading cause of death for PLHIV globally. Findings from a study among PLHIV in Latin America, presented at CROI 2019, also suggest that PLHIV diagnosed with TB at initial clinic visit were about twice as likely to die within 10 years as people not initially diagnosed with TB. These findings underscore the need for TPT. Shortening duration of TPT is also associated with better completion rates and is cost effective. Thus, Lesotho is transitioning to combination prevention using Rifapentine and Isoniazid (HP). However, use Isoniazid alone (IPT) will continue as indicated below until formal transition to HP is made.
Given the high prevalence of HIV and LTBI in Lesotho, clinicians should always remember to:

- Provide information about TB, including TPT, to all HIV-infected patients who present for health services.
- Clinicians should also counsel patients about the benefits of taking TPT, side-effects associated with TPT, and need for adherence to TPT
- Provide TPT to all persons who are eligible.

TPT reduces the risk of progression to active TB disease among PLHIV. HIV-infected patients on ART are still at higher risk for active TB than HIV-uninfected persons and the risk of TB is particularly high during the first six months after ART initiation.

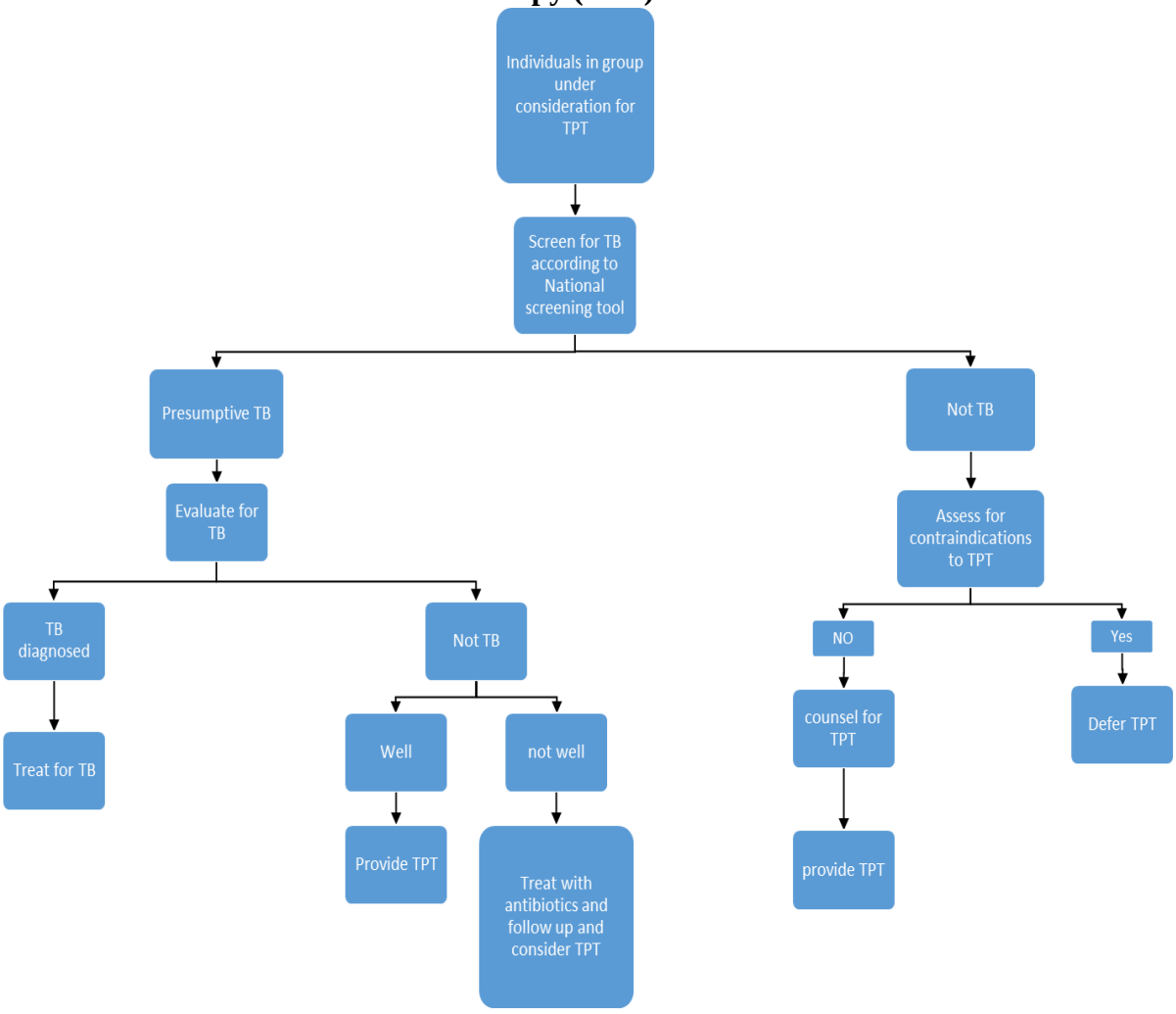
During post-test counselling following diagnosis of HIV, patients should be screened for symptoms of active TB and informed about the benefits of TPT. TPT is integrated within the HIV services provided by the HIV/ART clinics, MCH/ANC clinics and paediatric clinics.

At every clinical encounter, PLHIV should be screened for signs and symptoms of TB using the Lesotho TB Screening Tool. Those who do not report any symptoms of TB are highly unlikely to have active TB and should be offered TPT if they have no contraindications to TPT. Those with one or more signs or symptoms of active TB are considered to be Presumptive TB patients and must undergo further investigations for active TB disease. Presumptive TB patients are not eligible for TPT until active TB has been excluded. Once TB has been excluded, TPT should be initiated and the patient should be followed up closely.

Eligible HIV-infected patients should be initiated on TPT irrespective of the CD4 count, WHO clinical stage, and ART status. Those who are already on ART and in whom active TB has been excluded should be initiated on TPT. There is an additional protective benefit of concomitant use of TPT and ART. Patients who are receiving TPT and who are eligible for ART should continue

TPT while initiating ART. TPT should not delay ART initiation among eligible PLHIV. The algorithm below summarises the approach to TPT in Lesotho

Algorithm for Tuberculosis Preventive Therapy (TPT)



Indications for TPT

All PLHIV greater than 12 months should be screened using the screening tool to determine eligibility for TPT. The box below summarises the indications for TPT in Lesotho.

Box 2

PLHIV

- All PLHIV ≥12 month in whom active TB diseases has been excluded as part of

comprehensive HIV care

- All HIV-positive infants < 12 months who have been exposed to TB through household contact, in who active TB has been excluded
- All PLHIV treated for TB immediately after completion of TB treatment or soon after

HIV-Negative

- All HIV-negative children under fifteen (0 – 14) years, including infants < 12 months, who have been exposed to TB through household contacts in whom active TB has been excluded
- All patients with silicosis in whom active TB disease has been excluded
- All Health care workers in whom active TB disease has been excluded

Box 3

Initiate TPT after:

- Active TB has been excluded.
- Contraindications to TPT (i.e. active TB disease, active hepatitis, alcoholism, severe peripheral neuropathy, epilepsy, or kidney failure) have been excluded.
- Patients have been counselled on the benefits of TPT, the importance of adherence to TPT, importance of completion of TPT and on the need to return should possible side-effects or signs/symptoms of TB develop.

Contraindications to TPT

HIV-infected patients with signs and/or symptoms of TB, or with signs and/or symptoms of active liver disease should not be offered TPT.

Patients should not be offered TPT if they report:

- Acute or chronic liver disease. Signs and symptoms suggestive of active hepatitis are: nausea, vomiting, right upper quadrant pain, jaundice, dark urine.
- Regular and heavy alcohol consumption.
- Symptoms of severe peripheral neuropathy
- History of epilepsy or convulsions.
- Kidney failure.

The absence of baseline liver function tests should not preclude the initiation of TPT. However, all HIV-infected patients should have a baseline lab assessment, the most recent ALT result should be reviewed if available.

Table 18: Interpretation of ALT levels in the context of initiating TPT

Baseline Liver Function Tests	Course of action
Normal up to 2x the upper limit of normal (ULN) in the absence of symptoms of hepatitis	Initiate TPT, no further testing required

2-5x the ULN in the absence of symptoms of hepatitis	Initiate TPT Check ALT monthly
Greater than 5x the ULN and/or symptoms of hepatitis	Do not initiate TPT

The standard options for TPT regimen in Lesotho are:

Rifampicin and Isoniazid Preventive Therapy (RH)
Children not eligible for HP (i.e. < 2 years)
Rifampicin and Isoniazid (RH 75/50mg):
2 – 3.9 kg = ½ tablet
4 – 5.9 kg = 1tablet
6 – 7.9 kg = 1½ tablets
8 – 10.9 kg = 2 tablets
11 – 14.9 kg = 3 tablets
15 – 19.9 kg = 4 tablets
20 – 24.9 kg = 5 tablets
Pyridoxine (Vitamin B6): 12.5-25 mg/day x 3 months

Rifapentine and Isoniazid combination (HP) - 12 doses
Isoniazid (INH)
Higher dosages of INH are used in this regimen as follows:

Adults: 15mg/kg/weekly (max 900mg) x 3 months
Children: 2 – 11 years 25mg/kg/week (max 900mg) x 3 months
Children: ≥12 years 15mg/kg/week (max 900mg) x 3 months

Rifapentine
For both Adults and children, rifapentine dosing is weight based as below; max 900mg:
10.0 – 14.0 kg = 300 mg
14.1 – 25.0 kg = 450 mg
25.1 – 32.0 kg = 600 mg
32.1 – 50.0 kg = 750 mg
> 50 kg = 900 mg

Isoniazid Preventive Therapy
Lesotho has transitioned out of use of IPT. For patients still on IPT, Pyridoxine should be given concomitantly with isoniazid to prevent the occurrence of peripheral neuropathy. However, patients should not be denied IPT due to non-availability of pyridoxine. Isoniazid preventive

therapy should be given once daily for 6 months. Strict adherence to IPT is essential. If a patient has an interruption in IPT for no more than three months, he/she can be restarted if still asymptomatic. Thus in case of interruption of less than 3 months, the treatment can be completed over 9 months.

Rifampicin and Isoniazid (RH)

RH is also a short-course TPT regimen that combines two antibiotics active against TB, INH and RIF. Rifampicin and isoniazid combination is taken once daily, for 12 weeks (90 doses in 3 months). The WHO LTBI guidance document released in early 2018 describes the 3RH regimen as an alternative option to 6H, for treatment of LTBI in children and adolescents <15 years of age, in countries with high TB incidence. However, the shorter 3RH regimen for children offers benefits for patients and health systems. Several studies have demonstrated that 3RH is better tolerated, with fewer side effects and better adherence than 6 months of isoniazid alone.

Drug-drug interactions in patients on ART

No dose adjustments required for efavirenz containing regimen. For individuals taking lopinavir/ritonavir, dolutegravir or nevirapine, dose adjustment of the antiretroviral drug is necessary as rifampicin is a cytochrome system enzyme inducer.

Weekly rifapentine and isoniazid for 3 months (12 doses)

Studies have shown that there is no significant difference in the incidence of TB between those on 3-month weekly regimen of rifapentine plus isoniazid and 6 months of isoniazid monotherapy. However, risk of hepatotoxicity is significantly lower in HP compared to IPT. Weekly HP regimen can be safely given with DTG although caution must always be taken. The regimen is also associated with higher completion rates

Drug-drug interactions in patients on ART

- Use cautiously in patients on DTG containing regimens. Double the dose of DTG by increasing frequency from once a day to **twice a day**.
- Adjust EFV dose from 400mg to 600mg
- Do not use rifapentine in PLHIV on protease inhibitors or Nevirapine

Monitoring patients on TPT

Patients on TPT should be monitored through monthly clinical assessment that includes:

- Screening for symptoms and signs of active TB (i.e. cough of any duration, fever, night sweats or weight loss).
- Screening for possible side-effects of isoniazid or rifapentine (e.g. rash, peripheral neuropathy, convulsions, or any signs/symptoms of hepatitis including nausea and vomiting, jaundice, right upper quadrant pain and dark urine).
- Adherence to TPT.

If a patient on TPT develops symptoms of active TB or possible side-effects due to isoniazid or rifapentine:

- Discontinue TPT immediately
- Investigate for active TB disease:
    - Send sputum specimen (morning) for GeneXpert Ultra
    - Refer if needed to ensure that investigations are completed
- If active TB is confirmed, a full TB treatment regimen should be started
- Perform other laboratory investigations as clinically indicated (e.g LFTs for those with symptoms of hepatotoxicity))

Routine laboratory monitoring of liver function tests (e.g. ALT) is not required during TPT. However, if a patient is known to have an elevated ALT at baseline (2-5x ULN), then monthly monitoring of the ALT is indicated. An ALT should also be ordered if symptomatic hepatitis develops while on TPT. If the ALT is greater than 5x the ULN, then TPT should not be restarted and the patient should be referred for further investigations.

All other laboratory tests should be ordered as clinically indicated.

Although HP regimen is associated with higher risk of adverse pregnancy outcomes, isoniazid (INH) is safe in pregnancy and during breastfeeding. TPT should be offered to all eligible HIV-infected pregnant and breastfeeding women after TB screening and exclusion of active TB. TPT can be started at any time during pregnancy. In the event that a woman on IPT becomes pregnant, TPT should be continued. Following delivery, TPT should be continued during breastfeeding to complete the six month course of therapy

TPT provides protective benefit to patients who have successfully completed TB treatment.
All HIV-infected patients should take TPT for three months immediately after completion of TB treatment based on regimen.

Infection Control (IC)

Persons with undiagnosed, untreated and potentially contagious TB are often seen and managed in health care settings; such frequent exposure to patients with infectious TB disease may put the health worker at risk. Furthermore, HCW and staff may be immunosuppressed themselves due to HIV infection and be at higher risk of developing TB disease.

Nosocomial transmission of *M. tuberculosis* has been linked to close contact with persons with TB disease during aerosol-generating or aerosol-producing procedures, including bronchoscopy, endotracheal intubation, suctioning, other respiratory procedures, open abscess irrigation, autopsy, sputum induction, and aerosol treatments that induce coughing.
All health facilities should be made aware of the need for preventing transmission of *M. tuberculosis* especially in settings where persons infected with HIV might be encountered or might work. All HCWs should be sufficiently informed regarding the risk for developing TB disease after being infected with *M. tuberculosis.*

All health-care settings should develop a TB infection-control plan designed to ensure prompt detection, airborne precautions, and treatment of persons of confirmed TB disease. TB infection

control measures can be divided into three categories namely: managerial/administrative, environmental (or engineering), and personal respiratory protection controls.

Administrative and Managerial Control: The first and most important level of infection control is the use of administrative and managerial measures to prevent droplet nuclei from being generated, thus **reducing the exposure** of HCWs and patients to *M. tuberculosis*. These measures include:

- Implementing effective written policies and protocols to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB
- Designating an Infection Control Committee/Officer in health facilities with responsibility and authority for the implementation of the infection control plan
- Assessing the risk for TB transmission in the facility should be conducted periodically
- Ensuring the timely processing of patients' screening, laboratory testing, and reporting of results to the ordering clinician
- Implementing effective work practices among HCWs for the management of patients with presumptive or confirmed TB disease
- Educating, training, and counselling HCWs about TB, with specific focus on prevention, transmission, and symptoms
- Screening and evaluating HCWs who are at risk for TB disease or who might be exposed to *M. tuberculosis* for TB infection and disease
- Ensuring that HIV-infected HCWs and support staff do not work in areas of high TB transmission or with MDR-TB patients

Environmental control measures: The following environmental control methods should be used in the above-mentioned high-risk areas to prevent the spread and **reduce the concentration of droplet nuclei in the air**.

- Maximizing natural ventilation e.g. keeping windows and doors open (even in winter and at night)
- Controlling the direction of airflow e.g. strategically placed fans

Ventilation maintains air quality by both air dilution and removal of airborne contaminants. Uncontaminated supply air mixes with contaminated room air (dilution), and air is subsequently removed from the room.

Personal respiratory protection: HCWs need to **be protected from inhaling infectious droplets** by the use of personal respiratory protective devices designed to fit over the mouth and nose and filter out infectious TB particles. The emphasis of infection control rests on maximising the environmental control and personal caution. Therefore, personal respiratory protection using **N95** or **FFP-2** respirators is indicated in specialized settings, e.g. sputum induction, referral facilities nursing MDR-TB and XDR-TB patients, and only when all other infection control measures have been fully implemented.

Development of an infection control plan for each health facility: Each health facility needs to develop an IC plan outlining:

- The people responsible for the implementation of IC activities (or IC control team) and their responsibilities

- Policy areas involved
- Description of the different interventions
- Actual IC work plans with clearly defined activities, persons responsible and indicators with timeframe
- M&E matrix with selected indicators to monitor the implementation of the IC plan

Roles of individuals in TB IC
TB IC is a way of life and a team approach. Every individual counts and should play a role.

Facility in-charge should

- Ensure facility has a written TB IC plan
- Ensure supplies and equipment are available and maintained
- Arrange facility space and patient flow to reduce TB transmission

Infection control focal person

- Develop TB IC plan
- Ensure consulting and patient waiting rooms are well ventilated
- Conduct on-site training on TB IC
- Monitor TB in HCWs and keep records
- Monitor TB IC practices daily

Layworkers/TB screeners

- Monitor patients in the waiting area and identify coughing patients promptly
- Give coughing patients tissues or surgical masks promptly
- Provide disposal bins for used tissues
- Separate coughers
- Prioritize coughers to see consulting clinician or nurses quickly

Consulting clinicians and nurses

- Screen patients for TB
- Evaluate presumptive TB cases and treat TB patients promptly
- Use PPE (N95 masks) when in high TB risk environments

Patients

- Observe cough etiquette (cover mouths and nose when coughing)
- Dispose of used tissues in waste bins
- Wear face masks when advised to
- Take TB medicines as prescribed

Laboratory staff

- Ensure results are returned to consulting clinician or nurse quickly
- Observe good TB IC practices

All individuals (HCWs and clients)

- Seek care promptly if they think they might have TB
- Think TB IC always and make it a way of life

TB/HIV Co-Infection: Clinical Presentation

The clinical picture of TB varies with the level of immunity of the patient. PLHIV are more likely to present with sputum smear-negative PTB, disseminated TB, or EPTB, especially as the

immunosuppression progresses. Therefore, a high index of clinical suspicion is needed to avoid misdiagnosis or delays in TB diagnosis, which may lead to increased morbidity and mortality.

Diagnosing HIV in TB Patients

All presumptive TB cases and TB patients should be offered HIV counselling and testing by HCW as a standard package of care. Individuals must specifically decline the HIV test after receiving pre-test information if they do not want the test to be performed. The HIV testing should be done according to the approved national HIV testing protocol and appropriate post-test counselling should be offered, with a strong focus on HIV prevention for those who test negative.

The provision of HIV testing by the HCW who provides TB services (or in the same facility) enhances the uptake of HIV testing for TB patients. HIV testing is best offered as soon as presumptive TB is identified. Documentation of the HIV test is crucial, and the result should always be documented in the Presumptive TB Case Register.

Clinical Assessment in TB/HIV Co-Infection

All TB/HIV co-infected patients should be provided with comprehensive clinical assessment prior to initiation of treatment. The assessment should include:

- A review of patient history
- Physical examination
- Laboratory investigations:
    - Full blood count
    - CD4 cell count
    - Pregnancy test for women
    - Liver Function Test-ALT
- Others (as determined by the patient's presentation)

However, it should be noted that lack of capacity to perform CD4 cell counts should not be a barrier to initiate HIV treatment for the TB/HIV co-infected patients. CD4 count is no longer a factor used to determine ART eligibility for TB/HIV co-infected patients. But attempts should always be made for baseline CD4 counts for monitoring purposes. Follow the test and start policy.

6.6.1 Lipoarabinomannan antigen in urine

Tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests for tuberculosis (TB). LAM antigen is a lipopolysaccharide present in mycobacterial cell walls, which is released from metabolically active or degenerating bacterial cells and appears to be present only in people with active TB disease. Urine-based testing has advantages over sputum-based testing because urine is easy to collect and store, and lacks the infection control risks associated with sputum collection. LF-LAM has sensitivity of 50 – 70% depending on CD4 count.

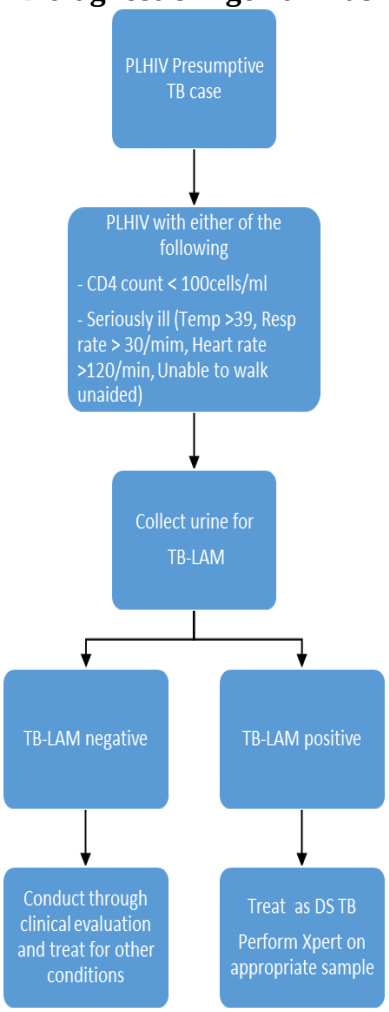
Indication:

It will be used in the diagnosis of both pulmonary and EPTB in HIV positive adults and children with presumptive TB

- who have a CD4 cell count of less than 100cells/Ml
- who are seriously ill regardless of CD4 cell count or have unknown CD4 count

Seriously ill is defined based on 4 danger signs; respiratory rate >30/min, temperature >39°C, heart rate >120/min and unable to walk unaided

National TB diagnostic Algorithm using LF-LAM



Treatment of TB in PLHIV

TB treatment is effective for both HIV-infected and uninfected persons alike. The same regimens used for HIV-uninfected persons should apply for the HIV-infected patients, with the same duration of treatment. There is a need for prompt initiation of TB treatment because of the increased morbidity and mortality associated with dual infection.

Enhanced DOTs (DOTs support for TB and HIV by same treatment supporter) should be provided to the patients with TB/HIV co-infection, while comprehensive adherence preparation

needs to be availed both to the patient and treatment supporter. This is in view of the increased morbidity and mortality (especially in the initial two months of treatment initiation), increased pill burden, and overlapping side effects from concurrent ARVs and anti-TB medicines.

Reducing HIV Burden in TB Patients

Integration of both TB and HIV services is critical for provision of a comprehensive package of dual services, but in settings where integration is not yet implemented, effective referral mechanisms between TB and HIV services should be established and maintained to ensure both services are provided to co-infected patients.

TB and HIV interventions should be introduced at all levels within the district health system as indicated in table 9 below.

Table 9: TB and HIV interventions at various levels of the health system

LEVEL OF HEALTH CARE	TB/HIV INTERVENTIONS
HOME AND COMMUNITY Community based organizations, NGOs, faith based organizations, government community health programmes	• IEC activities regarding TB, HIV, and STI Condom promotion • Nutritional advice and support • Psychological support • Community DOT for TB • Community-based palliative and terminal care
PRIMARY CARE Government health centres or clinics, mission health centres, NGO health centres, private health centres	• HTC and HIV prevention • Intensified TB case finding and treatment • • TPT/Cotrimoxazole provision • Condom promotion • STI syndromic management • Management of HIV related opportunistic infection and palliative care • Prevention of mother to child transmission • ART
SECONDARY CARE Government hospitals, mission hospitals, private hospitals	• Diagnosis and treatment of HIV-related diseases • In patient palliative care • Diagnosis and management of complications or severe presentations of TB/HIV disease

CTX

In all HIV-infected TB patients, cotrimoxazole preventive therapy should be initiated as soon as possible and given throughout TB treatment. Cotrimoxazole preventive therapy substantially reduces mortality in HIV-infected TB patients. Cotrimoxazole prophylaxis is contraindicated in patients with history of a sulfa allergy. In such patients, dapsone will be used instead. It should be used cautiously in patients with pre-existing renal or hepatic insufficiency.

Dosage:

- Cotrimoxazole 960mg daily

If there is a cotrimoxazole allergy:

- Dapsone 100 mg/daily (child 2 mg/kg/day)

HIV Prevention in TB patients

The recommended package for HIV-related prevention, treatment, care and support services for PLHIV should be provided for TB patients in TB clinics. To improve treatment success, the needs of particular groups (e.g., prisoners, migrant workers, other high risk groups) should be assessed and addressed through integration with other services.

HIV treatment for TB/HIV co-infected patients

TB/HIV co-infected patients have an increased risk of dying before TB treatment is completed, and fatality occurs mainly in the first two months of TB treatment. There is need to fast track these patients for both TB and HIV care and treatment alike. Delaying ART initiation increases the mortality due to HIV infection. Early initiation on ART while on TB treatment will reduce mortality and morbidity among HIV co-infected TB patients. Improved immune system functioning from ART helps to cure TB and decreases infectiousness and transmission of HIV.

Even though co-treatment is associated with drug-drug interactions, overlapping toxicities, pill burden with risk of poor adherence, and increased frequency of immune reconstitution inflammatory syndrome (IRIS), the reduced morbidity and mortality accruing from early initiation of ART far outweigh any adverse events.

When to start ART in TB/HIV co-infected patients

All TB/HIV co-infected patients should be started on ART within 2-4 weeks of TB treatment initiation, irrespective of the CD4 cell count. Clinical assessment is the primary tool for evaluating patients both before TB treatment initiation and after ART treatment has been initiated. Laboratory investigations can help inform which regimen to choose but are not essential for ART initiation. Inability to perform laboratory investigations should not prevent patients from being initiated on ART.

Comprehensive patient preparation should be provided in view of the needed adherence to both TB and HIV treatments. Adherence counselling should be offered on an ongoing basis.

Box 4

All TB/HIV co-infected patients should be initiated on ART within 4 weeks of starting TB treatment.

What ART regimens to use for TB/HIV co-infected patients

The choice of ART regimen for TB patients is guided by available evidence on effectiveness, drug availability, overlapping side effects, and toxicity profiles. These regimens are well covered in ART guidelines 2018

The current recommended 1st-line ART regimen for adults is TDF + 3TC + DTG (TLD). In patients on Rifampicin based regimen, dosage of DTG should be doubled to 50mg twice a day.

Efavirenz (EFV) is the preferred NNRTI in patients on TB treatment. In such patients the regimen is TDF + 3TC + EFV_{600} (TLE)

Table 10: ART for TB/HIV co-infected patients

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
Tenofovir(TDF) Lamivudine (3TC) Zidovudine (AZT) Abacavir (ABC)	Efavirenz (EFV) 600mg Nevirapine (NVP) – in children < 3 years and < 10kg

Alternative regimens include AZT + 3TC + EFV and ABC + 3TC + EFV. The preferred 1st line ART regimen for children and ABC + 3TC + EFV (LPV/r if <3 years or <10 kg).

Patients who Develop TB while on ART

If TB is diagnosed after a patient has already been initiated on ART, then TB treatment must be started, and the following options considered:

- Adults who are on Nevirapine-based regimens, switch to Efavirenz 600mg.
- Adults on LPV/r or other PIs: There are significant interactions between PIs and rifamycins and should not routinely be used together. There may be situations when LPV/r is the only option for patients on concomitant TB treatment, in which case it should be used. If a patient is on LPV/r already,
    - *add Ritonavir (RTV) to obtain a LPV:RTV ratio of 1:1 necessary to achieve the full therapeutic effect of the PI.*
    - *Or double dose of LPV/r from 400/100mg bd to 800/200mg bd*

Dosing using a 1:1 ratio of LPV:RTV has been associated with increased toxicity compared to doubling of the dose. The doubled dose should therefore be used preferentially.

Drug-Resistant TB and HIV

Drug-resistant forms of TB (such as MDR-TB and XDR-TB) have been reported to be more common among HIV-infected populations in some studies. Thus, any patient not clinically or bacteriologically responding to TB treatment after two months who is receiving good DOT should have molecular DST done using GeneXpert and specimen sent for culture and phenotypic DST. For management of patients with suspected or confirmed drug-resistant TB, please refer to Chapter 9: Drug Resistant TB.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Following the initiation of ART, the immune system is reconstituted and begins to respond to antigens more vigorously. IRIS is a phenomenon that occurs when a patient on ART begins to have immune recovery in the presence of an untreated or partially treated OI.

TB IRIS can present in two ways.

- Paradoxical TB IRIS – a patient is diagnosed with TB, starts TB treatment followed by ART after a few weeks, and then develops worsening TB signs and symptoms.
- Unmasking TB IRIS – a patient is screened for TB before initiation of ART and no TB is found. The patient then starts ART, followed by onset of TB symptoms and signs.

TB IRIS usually occurs within the first 2-12 weeks of initiating ART.

The key risk factors for IRIS include the following:

- Severe immune suppression (CD4 count <50)
- High viral load (>100,000 copies/ml)
- Early initiation of ART
- Marked rise of CD4 count and fall of viral load following ART initiation
- Presence of subclinical opportunistic infections

Management of IRIS is to continue TB treatment and provide non-steroidal anti-inflammatory drugs (NSAIDs). Corticosteroids may be used in cases with severe signs. Admit all patients with danger signs. In general, do not stop ART! The possibility of IRIS should be explained to patients prior to initiation of ART (i.e. the patient may become worse before becoming better).

Danger signs include, but are not limited to:

- Respiratory distress (RR > 30)
- Fever ($T>39^0$)
- Tachycardia (HR > 120)
- New or worsening adenitis, with obstructive symptoms

IRIS is a diagnosis of exclusion and particular attention should be paid to assess/exclude the following:

- TB treatment failure or drug resistant TB
- ART treatment failure
- Other opportunistic infections
- Side effects of TB treatment and/or ART
- Drug fever
- Other HIV-related diseases (lymphoma, Kaposi's Sarcoma)

Control of TB Transmission in Prisons

Tuberculosis occurs up to 100 times more commonly in prisons than in civilian populations.

- The spread of TB is worsened by late diagnosis and treatment of infectious cases, and poor prison living conditions such as overcrowding

- The main strategies for achieving these goals of TB control are the early diagnosis of TB cases and their prompt and effective treatment.
- It is thus vitally important to screen new inmates by history and sputum examination if the inmates are symptomatic for TB.
- Penal reforms and improvement in prison living conditions are also important strategies for early case detection, rapid effective treatment which will reduce morbidity and mortality in prisons and so interrupt the chain of transmission
- There should be "Equivalence" of care in the prisons, i.e. all prisoners have the right to the same standard of health care as the state provides for the general community
- There should be particular attention on integrating prison and civilian TB services.

ADHERENCE AND PSYCHOSOCIAL SUPPORT (APS) ACTIVITIES FOR TB AND TB/HIV CO-INFECTED PATIENTS

Management of TB requires a chronic-care approach, supporting patients to achieve cure. The goal of the National TB Programme is to reduce mortality rate due to TB in line with the Sustainable Development Goals and global TB control targets. Education and participation of TB patients, their treatment supporters and communities in TB care will contribute to the increase in treatment success from 74% to 90% and to the reduction of mortality among TB patients during treatment to less than 11%. The adherence and psychosocial support (APS) activities seek to build on existing community-based care systems, to improve patient and treatment supporter knowledge in order to enhance adherence to treatment.

Promoting Adherence to Medication and Care Plan

HIV-Uninfected Patients

Education to be provided to HIV-uninfected patients and their DOT supporters at initiation of TB Treatment involves the topics outlined below.

Group education or individual counselling session divided into two sessions:

- **Definition:** Tuberculosis or TB is an illness caused by germs that are breathed into the lungs. TB germs can settle anywhere in the body, but most commonly affect the lungs. When the lungs are damaged by TB, the person coughs up sputum (mucus from lungs) and cannot breathe easily. Without correct treatment, a person can die from TB.
- **Transmission:** TB spreads when an infected person spits sputum in an open space, coughs or sneezes, spraying TB germs into the air. Others may breathe in these germs and become infected. It is easy to pass germs to family members when many people live closely together. Anyone can get TB. However, not everyone who is infected with TB will become sick.
- **Persons at increased risk of TB infection/disease**: Persons who have been recently infected with TB, close contacts of a person with infectious TB disease (especially children less than 5 years), persons who work or reside with people who are at high risk for TB in facilities or institutions such as military barracks and correctional facilities, and persons with medical conditions that weaken the immune system are at increased risk of acquiring TB infection and disease.
- **Discussion on myths/misconceptions about TB:** Learn about the patient's beliefs and attitudes about TB and treatment. Positive attitudes and beliefs support adherence. Patients tend to adhere better to treatment if they believe that treatment is beneficial, are able to make a commitment to long-term treatment, and are confident that they will be able to take medications correctly and regularly.
- **Signs and symptoms of TB**: Any person who says they have either a cough, night sweats, fever, or loss of weight, may have TB disease and should be seen by a HCW. For

children, being in contact with someone who has TB increases their chance of having TB disease.

- **How to prevent spread of TB**: Cover mouth and nose when coughing and sneezing, proper disposal of sputum, open windows and doors to allow fresh air through the house, identification of exposed contacts, early detection of TB, adherence to TB treatment for cure.
- **Importance of screening household contacts and infection control:** This will minimize the transmission of TB within the community. Finding persons who have active TB disease early so treatment can be given, further demises TB transmission. Provide all children < 15yrs who are contacts of pulmonary TB cases and HIV-infected children with TB preventive therapy. Refer HIV-infected contacts for Tuberculosis Preventive Therapy (TPT).
- **How long TB medications are taken**: At least 6 months. Longer courses may be needed depending on site of disease and presence of drug resistance. Patients need to come for their refill/check-up appointments and monitoring tests at scheduled times.
- **Potential side effects:**

Table 21: Potential side effects and suggested management

Drug Name	Minor Side Effects	Management
Isoniazid	Nausea, abdominal pain	Take drugs with food
Isoniazid	Burning sensation in feet	Consult clinician without stopping medication
Rifampicin	Orange/red urine	Reassure patient that this is expected
Isoniazid	Itching of skin, skin rash	Consult clinician immediately
Isoniazid, Pyrazinamide, Rifampicin	Yellow skin or eyes, vomiting repeatedly	Consult clinician immediately
Ethambutol	Difficulty with vision	Consult clinician immediately

- **When TB medications should be taken:** TB drugs are taken once daily, preferably at the same hour each day, e.g.,.8.00 a.m.
- **What happens when one misses doses:** Patients are advised not to miss doses because this increases chances of developing resistance to TB medication. Patients need to report any missed doses and document in TB card for compensation at the end of phase.
- **Importance of completing the doses:** To eradicate TB bacteria in a person's body, to avoid development of resistance to TB medication, to prevent further transmission of TB to other people, and to ensure TB patients are cured.
- **TB medications are taken under direct observation (DOT**): DOT is defined as Directly Observed Treatment: an appointed agent directly monitors people swallowing their TB medications. It seeks to improve adherence of people to TB treatment, thus resulting in cure.
- **Identification of DOT supporter:** TB treatment requires observation by DOT supporter, therefore patients must identify suitable individual in the community who could serve this role. The Community Health Worker (CHW) will supervise the DOT supporter and report to the health facility.

- **Qualities of DOT supporter:** The role requires a person who is convenient and acceptable to the patient and must be able to be supervised by CHW. They need to be trained by health care workers to perform the tasks of a DOT supporter. They must be kind and interested in patient's welfare, be careful in administering medications and documenting in patient's treatment card, and be able to follow up if any problems occur or if the patient does not come for appointments.
- **Roles of DOT supporters:** To ensure that patients take their medication as discussed. To support the patient's adherence to treatment for the entire duration, to encourage the community to take responsibility in TB treatment as this support will also help to combat TB. To screen household contacts of all TB patients allocated to them and refer those who are sick to the health facility.
- **Patients' role during TB treatment:** Providing authentic/correct information, adhering to treatment, attending appointments, seeking support and keeping up with health-related documents.

HIV-Infected Patients

Education for TB/HIV co-infected patients and their DOT supporters at TB Treatment initiation
1st session of ART preparation in individual session.

In addition to the above listed components for TB education, the following aspects need to be addressed through individual counselling:

- **Definitions of HIV and AIDS:** HIV is a virus that attacks a person's immune system, and can hide for long periods of time in the CD4 cells of your body. Your body needs these cells to fight infections and disease, but HIV invades them, uses them to make more copies of it, and then destroys them. Over time, HIV can destroy so many of your CD4 cells that your body can't fight infections and diseases anymore. When that happens, HIV infection can lead to AIDS. *Acquired Immunodeficiency Syndrome (AIDS)* is the final stage of HIV infection. People at this stage of HIV disease have badly damaged immune systems, which put them at risk for *opportunistic infections (OIs)*.
- **Modes of transmission:** Unprotected sex with someone who has HIV through semen and vaginal secretions; through blood contamination e.g. Sharing sharp objects such as needles, syringes; being born to an infected mother—HIV can be passed from mother to child during pregnancy, birth, or breast-feeding.
- **Prevention:** Engaging in protected sex using condom at every engagement of sexual intercourse, avoid contact with other people's blood and body fluids i.e. wearing gloves, testing for HIV infection during pregnancy so that proper care can be given to both mother and baby to prevent transmission of HIV
- **Opportunistic infections**: These are the infections that take advantage of weakened immune systems. Some of the most common opportunistic infections include TB, PCP, chronic diarrhoea and cryptococcal meningitis.
- **Relationship between TB and HIV:** Together, HIV and TB are a deadly combination, each disease making the other disease progress faster. HIV makes the immune system weak, so that someone who is HIV-positive and also harbours TB infection has increased chances to manifest with active TB than someone infected with TB who is HIV-negative.

- **Eligibility for ART in TB patients:** The recommendation is that all patients who are HIV/TB co infected need to be initiated on ART within 2-8 weeks of ATT commencement regardless of their CD4 count

Who will do the sessions?
Depending on individual facilities, any of the following:
- Lay counsellors
- Health educator
- TB Officer
- Nurse

Where?
Depending on model of integration, any of the following:
- TB clinic
- ART clinic
- OPD
- MCH
- Hospital Wards

When?
- **1st session:** At initiation of TB treatment
- **Provision of ongoing adherence and psychosocial support:** After 2 weeks and every month thereafter. Ensure same day appointments for the different services wherever possible

Ongoing Adherence Counselling and Support for TB Patients

Issues to address in group education or one- on-one individual counselling session:
- **Discussion on how the patient is taking his/her medication:** Use of all adherence aids such as pill count, pill chart, treatment card. Ask patient if there are any pills missed during the current month.
- **Identification of barriers to adherence:** These include but are not limited to: knowledge and understanding about HIV/AIDS and TB, attitudes and beliefs, lack of social support, mental health or psychological well-being, course of therapy, complexity (number of pills to be taken), difficult life conditions, system barriers
- **Discussion on any possible side effects**
  Patients taking TB medication may experience side effects such as sensations in their feet, itch and skin rashes, discoloration of urine and poor liver function. However, most patients will complete treatment without experiencing SE. Those that do, may experience mild forms of the side effects.
- **Discussion on family and community support systems including TB/HIV support groups:** Support groups for PLHIV and TB patients can enhance adherence by creating an environment where people can discuss how treatment is affecting their lives with other peers. A support group provides a ' welcoming environment' for PLHIV and TB patients, where they do not have to feel uneasy about speaking openly about what it is like to live

with HIV/AIDS and TB, or take ARVs/TB medicines. Through the groups, a patient may gain encouragement and knowledge from others who are experiencing similar challenges.

- **Strategies to address barriers identified:** proper patient education and preparation before initiation of ART and TB treatments, ongoing adherence counselling needs to be provided when clients come for clinic visits, have tools to support adherence i.e. pill boxes, pill counts, pill charts etc., patients' follow up system and peer support groups.
- **Next steps**: Develop a plan with the patient to address the identified problems/challenges

Preparing TB Patients for ART Initiation

Second Session: Individual session before or at week 2 of TB treatment

- **Review** of patient's understanding on information provided in 1st session
- **Names of ARVs most preferred in Lesotho:** Tenofovir (TDF), Zidovudine (AZT), Lamivudine (3TC), Dolutegravir (DTG), Efavirenz (EFV)
- **Benefits of ARVs:** to suppress the level of virus in the blood as much and as long as possible to restore and/or preserve immunological function to improve quality of life, and to reduce HIV-related morbidity and mortality. Lowers the risk of infecting others with HIV (by decreasing the viral load) and reduces mother-to-child transmission of HIV
- **How and when to take ARV and TB treatment:** TB and ART treatment can be taken concurrently.
- **Commitment to lifelong treatment:** HIV requires life-long therapy because ARVs are not a cure for HIV but rather delay progression in a person's body
- **Benefits of taking both ART and TB treatment concurrently:** less death and disability from either infection. TB is curable even when HIV positive.
- **Importance of good adherence:** Taking the right medication at the right dose at the right time and in the right way for the right duration (adherence) is one of the most important ways for patients to ensure that TB is cured.
- **Consequences of non-adherence:** The levels of drugs in the body drop and HIV or TB keeps multiplying therefore the CD4 cell count will drop and people will become more ill. People can develop resistance to one or all of the drugs, meaning that the drugs will not work anymore even if they are taken correctly again. This can lead to the development of MDR_TB, which is difficult and takes longer to treat. In addition, patients may remain with uncured TB, resulting in further transmission to other people.
- **Identification of potential barriers to adherence:** these include but not limited to: knowledge and understanding about HIV/ AIDS and TB, attitudes and beliefs, lack of social support, mental health or psychological well-being, course of therapy, complexity (number of pills to be taken), difficult life conditions, system barriers (drug stock-out)
- **Discuss ways to address barriers:** proper patient education and preparation before initiation of ART and TB treatments, ongoing adherence counselling needs to be repeated when clients come for clinic visits, have tools to support adherence i.e. pill boxes, pill counts, pill charts etc., patients' follow up system and peer support groups.
- **What to do when one misses doses for TB or ART treatment:** Patients are advised not to miss doses because this would increase the chances of developing resistance to TB and HIV medications. However, if the patient has missed dose at a specific time set for ART

treatment they should take the dose as soon as they remember. Patients need to report any missed doses and document in TB card, ART card and adherence form for compensation at the end of phase that the patient is on TB treatment.

- **Side effects and their management:**

Table 22: Side effects and their management

Drug Name	Side Effects	Management
AZT/Isoniazid	Anaemia (pale, weak, dizzy)	Consult clinician
Isoniazid	Burning sensation of feet/hands	Take pyridoxine; consult clinician if persists
NVP/Isoniazid	Skin rash	Consult clinician immediately
All ARVs and TB medicines	Headache	Rest in a dark, quiet room with eyes closed, but if persistent consult clinician
All ARVs and TB medicines	Nausea, abdominal pains and vomiting	Take drugs with food but if vomiting persistent consult clinician
EFV	Unusual or bad dreams	Avoid substance abuse and reduce intake of fatty foods; Take medication at bedtime
Rifampicin	Orange/red urine	Reassure patient that it is expected
Ethambutol	Difficulty with vision	Consult clinician immediately
Rifapentine	Cutaneous reactions, hepatotoxicity	Consult clinician

- **Importance of bringing all medication during clinic visit:** Because adherence is very critical in patient taking ART and TB treatment it is imperative for patient to bring their medication for pill count; this helps to assess patients' adherence so that required action can be taken.
- **Infection Control:** maintenance of proper ventilation, proper patient flow (Triage), patient education and community awareness, effective referral systems between services for timely TB screening for all patients coming for services in different departments and initiation of TPT for HIV-infected patients and TB exposed children <15years
- **Disclosure:** All patients should be encouraged to disclose their status to family, household members, and community members. Often times, appropriate disclosure can help a patient develop a reliable support network, which can be crucial to successful adherence. Furthermore, disclosure can help fight stigma and encourage others within the family and community to "know their status" and also get tested
- **Discussion on migrant status and travel**: discuss with patients if they have any plans of moving so that necessary arrangements could be made. Because ART is lifelong treatment which makes patients feel better and begin to have plans of moving, they need to know that health facilities are always there for them to make their life easier i.e. discussing treatment plan and transferring patient to nearby facility so there is no need for them to interrupt their treatment
- **Treatment supporter and other support systems**
  TB treatment supporter shares responsibility with patient for the successful completion of treatment. S/he provides therapy under supervision as well social and psychological support. Community at large through home based care system can augment this support but requires strong M&E. regular contact between supporters and the NTLP is essential for motivation.

Third Session of ART preparation

- Patient readiness assessment (individual session) at week 2-4 of TB treatment
- Reassessment of understanding of basic HIV knowledge and ART information: does the patient have basic information, does the patient understand his/her regimen, is the patient ready for lifelong commitment, etc.
- Encouragement of disclosure to family/other care givers who can support the patient's treatment plan
- Review of individual care plan
- Review adherence strategies
- Referral to the community for further support if needed
- Refer for initiation of ART

Provision of Ongoing Adherence and Psychosocial Support

After initiation of ART and every visit thereafter, there should be ongoing adherence counselling and support for TB/HIV co-infected patients.

Issues to Address in Individual Counselling Sessions

- Discussion on how the patient is taking his/her medication (TB and ART drugs) and coping with co-infection treatment
- Inquire if there are any pills missed in the current month
- Find out about reasons for missing the pills
- Discussion on any possible side effects
- Discussion on any other concerns/problems that the patient may be experiencing that may make him /her miss taking medications or attending other clinical appointments
- Discussion on family and community support systems including VHWs
- Discussion on any other challenges/problems faced by the patient
- Review of household contacts screening for TB
- Next steps/plan for the patient to address the identified problems/challenges

Home Visit and Supervision of DOT Supporter

- **Who?** TB Coordinator/Officer/Lay Counsellors LC/VHW/APSO
- **When?**
    - At least one home visit per month for every initiated TB patient during the course of his/her 6 months treatment
- **What issues to cover during Home Visits?**
    - All items in section 8.3 above and the following
    - **Health education on basic TB/HIV information:** definitions, transmission, prevention, relationship between HIV and TB (as discussed in above sections)

    - **Adherence assessment:** has the patient missed any dose, pill counting, checking that TB card is updated, identify factors that might affect patient adherence, employ strategies that could improve adherence
    - **TB screening of Households contacts and referral of all <15yrs to the facility:** VHW should screen all people living in the same households with TB patients using TB screening tool and document in TB contact tracing form. Patients that have been identified as presumptive TB case and all children <15 years need to be referred immediately to the health facility. This information has to be reported at monthly VHWs meetings.
- **Supportive supervision of DOT supporter:** in cases where patients are not supported by VHWs they need to identify DOT supporter based on previously discussed qualities and have them attend 2 weeks check up appointment so that they can be educated on their role and responsibilities. VHWs from a nearby village should conduct supervisory visits to support the DOT supporter at least once a month to ensure that patients are given treatment and health education accordingly; household contact tracing, infection control assessment, and adherence counselling are done.
- **Address any other needs**

Monitoring Adherence and Identification of Non-Adherence Using Adherence Monitoring Tools

Appointing and Documentation

- Appointment system is intended to make organization of the work at clinic easier as the provider would know ahead of time what patients he/she expects each day. Furthermore, it allows facility to identify patients that have missed appointments in time so that follow ups can be timely effected
- All follow-up visits given to patients shall be recorded in the appointment book at the end of the visit.
- Appointment book should be updated at all times.
- Patient shall be clearly informed on the date of the next visit
- The provider must ensure that patients understand when to return for the follow-up visit
- If patient does not come for an appointment, follow-up has to be done within 1 day (intensive phase) or 5 days (continuation phase) of missing appointment

Identity Patients that have missed their Appointment:

- Identify patients that have missed their appointments through use of appointment book
- Compile a list of patients who have missed their appointments within 1 day (intensive phase) or 5 days (continuation phase) of missing appointment of not showing up at the facility: confirm with the TB treatment cards and any other relevant documents before tracing
- Document missed appointments patients in patient tracking tool/missed appointment register

Follow-Up Actions for Missed Appointments:

- Missed appointment Lists/patient tracking forms submitted to VHWs, Lay counsellor, TBO for follow-up or any other personnel designated to conduct tracking and tracing
- Plan tracing missed appointments based on the patient desired/agreed plan
- Phone calls/SMS within 1 day (intensive phase) or 5 days (continuation phase) of missing appointment
- Message /information through VHWs/neighbours
- Home visit by any of the designated persons to conduct follow up
- Use the address offered on the patient card to guide you in your home visits
    - If the patient is not at home, try to find out from the neighbours where the patient is
    - If the patient is found, talk to him about reasons why she /he missed appointments and document in patient tracking tool
    - Offer adherence counselling and refer patient back to the health facility with a referral slip from tracking tool
    - Results/outcome of the tracking/Tracing process should be documented (TB register, Appointment book and tracking tool)
    - The referral slips should have a central place where they can be kept for facility reporting and tracking of their patients

Return to Care after Missed Appointment or Loss-to-Follow-Up:

- When patient presents with tracking referral slip, they need to be re-established into care and offered intensive adherence counselling to address the barriers identified. Counselling is an ongoing process therefore patients need to be provided with ongoing adherence counselling every time they visit health facility. Basic information regarding TB and HIV should be reviewed, but special emphasis is needed to address and overcome barriers to care.

Multidrug-Resistant Tuberculosis (MDR TB)

The exact extent of DR-TB in Lesotho is not known, but it is likely to be similar to neighbouring South Africa. WHO estimates that the prevalence of MDR-TB is 4.8% in new TB cases and 14% in previously treated TB cases and includes RR/MDR. TB. In 2008-2009, the drug resistance survey showed that 12.7% had resistance to isoniazid or rifampicin; 7.3% had any resistance to isoniazid and 6.1% had any resistance to rifampicin. Monoresistance to either isoniazid or rifampicin occurred in 5.6%, with the majority from isoniazid monoresistance, 4.2% versus rifampicin monoresistance 1.7%.

Because DR TB treatment is long, it is important to monitor interim treatment outcomes for better patient management. Preliminary treatment outcomes may also be assessed at 12 and/or 24 months to monitor patient progress. Sputum cultures should be performed monthly (every 30 days) during therapy.

For more detailed, approaches to management of DR TB Management, please refer to Lesotho Guidelines for Management of Drug Resistant Tuberculosis, Third edition 2019.

Table 11: Terms "conversion" and "reversion"

Outcome	Definition
Conversion	culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the specimen collection date of the first negative culture is used as the date of conversion
Reversion	culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive. For the purpose of defining *Treatment failure*, reversion is only considered when it occurs in the continuation phase

Groups at high- and medium-risk for DR TB: Several groups of individuals are more likely to be infected with drug-resistant strains of TB. All patients at high or medium risk for DR-TB should receive DST.

High and Medium Risk Groups:

- Migrant workers (e.g. South Africa)
- Health workers
- Treatment after relapse or default
- Household contact of known MDR-TB patient with new TB
- Probable treatment failure (bacteriological or clinical evidence of failure)
- History of treatment with second-line TB drugs

For these patients, send sputum for GeneXpert for rapid molecular diagnosis. Also send sputum for culture and DST. If no evidence of rifampicin resistance on rapid testing, begin treatment with DS TB Treatment regimen. If evidence of rifampicin resistance, begin empiric DR Treatment regimen. Therapy to be adjusted if needed based on DST results. For those with previously treated TB and no access to rapid testing, begin treatment with DR regimen and adjust therapy based on DST results.

Table 24: Description of high risk groups and necessary actions

Description of High Risk Group	Associated Action
Household contact of known MDR TB patient	Send sputum for GeneXpert • If rifampicin resistance is detected, begin DR TB Treatment regimen based on DST of index case • If rifampicin resistance is not detected, begin New TB Treatment regimen Adjust therapy based on DST results.
Probable treatment failure: Smear-positive in fifth month of new TB Treatment **or** HIV-infected and smear positive **or** lack of clinical improvement after intensive phase during New TB treatment	Send sputum for GeneXpert • if rifampicin resistance is detected, begin empiric DR TB Treatment regimen • if rifampicin resistance is not detected, continue current regimen Adjust therapy based on DST results. There are many reasons for clinical deterioration in TB/HIV co-infected patients. Call Clinical expert for advice.
History of treatment with second-line TB drugs	Start individualized MDR TB regimen based on previous DST results and past history of TB treatment. Adjust therapy based on DST results.

DST in Children

Children may not be able to produce sputum specimens on demand. However, every effort should be made to obtain appropriate specimens (sputum induction or gastric aspiration). Children should not be excluded from treatment solely because they do not have DST; smear- and culture-negative children with active TB who are close contacts of patients with DR TB can be started on empiric DR TB regimens in consultation with an expert.

Empiric Treatment for MDR TB

With increasing availability of rapid molecular methods of DST, empiric treatment should become less necessary. If rapid DST is not available, then high-risk patients should be treated empirically with an MDR regimen. When DST results are available, the treatment regimen may be changed accordingly.

Lesotho Standardized MDR TB Regimen

classification of TB drugs

This guide uses the new grouping of medicines based on the WHO 2019 Guidelines. The hierarchy is based primary on treatment efficacy but also considers toxicity, whether a DST exists for the drug to help guide the treatment, and resistance prevalence.

GROUP	DRUG	Abr.	Other important characteristics (Toxicity, DST availability, resistance

				prevalence)
Group A: Strongly recommended agents	Fluoroquinolones*	Levofloxacin Moxifloxacin	Lfx Mfx	Low toxicity; Genotypic and phenotypic DST reliable; Resistance can vary.
	Diarylquinolines	Bedaquiline	Bdq	Low toxicity; Phenotypic DST reliable but not widely available; Resistance is rare.
	Oxazolidinone	Linezolid	Lzd	**High toxicity (potentially irreversible);** Phenotypic DST reliable but not widely available; Resistance is rare.
Group B: Oral core agents		Clofazimine	Cfz	Low toxicity; Phenotypic DST reliable but not widely available; Resistance is rare.
		Cycloserine Terizidone	Cs Trd	**High toxicity;** No reliable DST exists; Resistance can vary.
Group C: Add-on agents		Ethambutol	E	Low toxicity; Never counted as an effective drug as DST is not reliable and resistance is very common.
		Delamanid	Dlm	Low toxicity; Phenotypic DST reliable but not widely available; Resistance is rare.
		Pyrazinamide	Z	Low toxicity; Never counted as an effective drug unless DST is done in a reliable laboratory and tests susceptible; Resistance is common in most settings.
		Amikacin†	Am	**High and irreversible toxicity;** IM or IV injection; difficult to implement; Genotypic and phenotypic DST reliable; Resistance can vary.
		Imipenem-cilastatin Meropenem	Ipm/Cln Mpm	Moderate toxicity; Always given IV **(difficult to implement programmatically);** Always give with Amx/Clv. DST not commonly available. Resistance is rare.
		Ethionamide Prothionamide	Eto Pto	**Poor tolerability**; Moderate toxicity; Rapid DST only picks up one of the mutations responsible for resistance (*inhA*); Phenotypic DST is poorly reliable; Resistance varies.
		High dose isoniazid	H^H	Evidence not formally evaluated in latest WHO review; DST is reliable; Not to be used if *katG* mutation is present; Never counted as an effective drug.
		Para-aminosalicylic acid	PAS	**Poor tolerability**; Moderate toxicity; No reliable DST available; Resistance is uncommon.

* Gatifloxacin was not evaluated in the IPD meta-analysis for the longer regimen. Gatifloxacin was used in some cohorts evaluated for the shorter regimen. No quality assured gatifloxacin is available.

† Only use if documented to be susceptible on LPA and high-quality audiometry is available (done at baseline and at least monthly while on Am).

Principles of MDR-TB regimen design and duration

• Regimens should be designed to have at least four drugs with either certain, or almost certain, effectiveness.

• If a drug is well tolerated, it is generally used throughout the whole treatment.

• Often, five initial drugs are preferred at the start when there is either uncertainty in one of the drugs or in order to make management of the regimen easier; if the patient develops intolerance

to one of the drugs in a five drug regimen, often the offending drug can be stopped and the regimen can still meet the minimum criteria of “at least four likely effective drugs”.
• Drugs with laboratory resistance should not be counted as "likely effective"; alternative drugs should be used in such cases.
• Drugs previously used as part of a failed regimen are unlikely to be effective, despite encouraging DST results. They may be ineffective because of undetected resistance, poor penetration or absorption. They may be added to the regimen of four preferably new drugs.
• Regimens should be designed based on the patient’s characteristics, TB history, and DST pattern of the infecting and index patient's strains. For example, while many regimens can be designed with the combination of Group A and B drugs, because of the high incidence of HIV in Lesotho, delamanid, a Group C drug, is often used to avoid drug-drug interactions with ART, decrease the chances of a toxicity that might occur with a Group A or B drug, or to replace a drug that is causing a drug toxicity.
• Linezolid can cause serious toxicity, including myelosuppression. Given that anemia is common in MDR-TB patients, linezolid should be used with caution if the haemoglobin is less than 8 g/dL.
• Treatment of adverse drug effects should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious side effects. Where side effects occur, priority should be given to treating the side-effects and avoid stopping the drugs. However, if the side effect is severe or life-threatening, the offending drug should be held or stopped, and another one substituted if stopping it results in less than four likely effective drug.
• If the side effect is moderate and there a reasonable alternative drug to make a substitution without compromising the regimen, drug substitution can be offered. This may improve adherence.
• The vast majority of patients should receive all oral regimens. Amikacin or streptomycin are only used when no oral alternative exists.

Standardised regimens for management of MDR-TB/FG-Resistant TB

Types of DR-TB	Regimen	Phases/duration of treatment
RR-TB/MDR-TB	Lfx-Bdq-Lzd-Cs-Cfz	6Lfx-Bdq-Lzd-Cs-Cfz/12Lfx-Lzd-Cs-Cfz
FQ-R TB/XDR-TB	Bdq-Lzd-Cs-Cfz-Dlm-Z	12Bdq-Lzd-Cs-Cfz-Dlm-Z / 6Bdq-Lzd-Cs-Cfz-Z

Extra-Pulmonary DR TB

Extra-pulmonary drug-resistant disease can present difficult diagnostic and treatment challenges. The ability to culture mycobacterium from extra-pulmonary sites is limited and thus the

diagnosis of MDR-TB and XDR-TB are difficult, as DST often cannot be performed. Furthermore, extra-pulmonary disease is more common in HIV-infected individuals and thus may be seen with increased frequency in Lesotho where most TB patients are also infected with HIV. Given the difficulty of obtaining specimens for culture and DST in patients with extra-pulmonary disease, clinicians should rely on patient history (i.e. prior treatment, exposure to a known MDR-TB or XDR-TB patient) and have a low threshold for instituting an empiric MDR-TB or XDR-TB regimen in at-risk individuals.

Extra-pulmonary DR-TB is treated with the same strategy and duration as pulmonary DR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with DR-TB, the regimen should use drugs that have adequate penetration into the central nervous system. Rifampicin, isoniazid, pyrazinamide, protionamide/ethionamide and cycloserine have good penetration into the cerebrospinal fluid (CSF); Amikacin does so only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration. The fluoroquinolones have variable CSF penetration, with better penetration seen in the later generations. There is limited experience with bedaquiline and delamanid for the treatment of TB meningitis. Clofazimine has been used extensively to treatment leprosy lesions in soft tissue; CSF penetration is probably poor. Linezolid is commonly used for osteomyelitis; penetration into bone and soft-tissues is excellent.

Monitoring of Treatment and Management of Side-Effects

Patients should be monitored closely for signs of both treatment failure and side effects. The best and most important way of monitoring response to treatment is through regular history taking and physical examination; objective laboratory tests often lag behind clinical response and are not sufficient on their own.

Monitoring progress of treatment:

Clinical response: The classic symptoms of TB—cough, sputum production, fever and weight loss—generally improve within the first few months of treatment and should be monitored regularly by health care providers. The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure.

For children, height and weight should be measured regularly (at least monthly) to ensure that they are growing normally. A normal growth rate should resume after a few months of successful treatment. For adults, weight should be recorded monthly. A height for all adults should be taken at the start of treatment and recorded on the treatment card. Without the height, Body Mass Index (BMI) cannot be calculated and nutrition status cannot be assessed.

Radiological response: The chest radiograph may be unchanged or show only slight improvement, especially in previously treated patients with chronic pulmonary lesions.

Chest radiographs should be taken at the initiation of treatment, every six months thereafter, and at the end of treatment, in case the patient subsequently develops symptoms.

Bacteriological response: The most important objective evidence of improvement is conversion of the sputum smear and culture to negative. While sputum smear is still useful clinically because of its much shorter turnaround time, sputum culture is much more sensitive and is necessary to monitor the progress of treatment.

Sputum examinations depend on the quality of the sputum produced, so care should be taken to obtain adequate specimens.

Persistently positive sputums and cultures should be assessed for Non-tuberculous (NTM)[2], as overgrowth with NTM in lung-damage secondary to TB could be common.

Sputum conversion is slower in DR-TB than in drug-susceptible TB. Paucibacillary culture results should not be automatically regarded as negative when treating DR-TB. Acquired drug resistance and treatment failure often begin with the growth of one or two colonies on a sputum culture. Culture conversion should not be equated to cure. A certain proportion of patients may initially convert and later revert to positive sputum culture.

Sputum smears and cultures should be monitored monthly. Culture conversion is defined as two consecutive negative smears and cultures taken at least 30 days apart.

For patients who remain smear- and culture-positive during treatment or who are suspects for treatment failure, DST to second-line drugs (Km, Cm, Oflx) can be repeated on any cultures four months or beyond to assess for XDR-TB.

Guidelines are provided by the national laboratory manuals for safe packaging and transportation of the samples. Sputum samples should be refrigerated during sample transportation and storage to reduce bacterial contamination during culture.

Monitoring for side-effects:

Patients should be closely monitored for side effects during treatment. The ability to monitor patients for side-effects daily is one of the major advantages of DOT over self-administration of DR-TB treatment.

The majority of side effects are easy to recognize, and patients report most side effects themselves. However, it is important to have a systematic method of interviewing since some patients may be reticent about reporting even severe side effects. Other patients may be distracted by one adverse effect and forget to tell the health care provider about others. Laboratory screening is necessary in detecting certain side effects that are occult (not obviously noted by taking the history of the patient or by physical examination).

There are two common occult side effects:

1. Nephrotoxicity is a known complication of the injectable (Amikacin and streptomycin)
2. Hypothyroidism is induced by PAS and ethionamide/prothionamide and is reversible after suspension of these drugs.

[2] Mycobacterium other than tuberculosis (MOTT) is also referred to as non-tuberculosis mycobacterium (NTM).

Table 26: Recommended laboratory monitoring

Sputum smear microscopy	Monthly
Sputum culture	Monthly
Drug susceptibility testing	Second-line DST is indicated on any cultures that are positive four months or beyond treatment.
Renal function tests (serum creatinine and potassium)	Every month while receiving injectable. Patients with baseline renal insufficiency should be monitored frequently.
Thyroid Stimulating Hormone (TSH)	Every three months
Liver serum enzymes	At baseline, then as clinically indicated for patients with symptoms of hepatitis.
HIV screening, CD4	At baseline. CD4 should be monitored every 6 months in HIV infected patients.
Viral load	
Pregnancy test (women of child-bearing age)	At baseline, then as clinically indicated. All women of child-bearing age should be provided with family planning counselling.
Full blood count	At baseline, then as clinically indicated.

Pregnancy testing should be done at baseline and whenever clinically indicated. If increased nausea and vomiting occurs in a woman of child-bearing age, consider morning sickness and rule out pregnancy. All DR TB patients should receive family planning counselling before starting treatment and should be strongly encouraged to use an effective contraceptive method.

CHILDHOOD TB

Introduction

Case notifications of childhood TB depend on the intensity of the epidemic, the age structure of the population, the available diagnostic tools, and the extent of routine contact tracing. Lesotho is a high TB incidence country. In such settings estimated TB incident cases generally represent 10 -15% of all adult cases. However, the proportion of notified childhood TB cases in Lesotho has consistently been below 5% in the last decade probably as a result of mis-diagnosis, under-diagnosis and under-reporting.

Children can present with TB at any age. Progression from infection to disease is highest in the six months after infection but remains high for two years. Risk of progression is increased when primary infection occurs before adolescence – particularly in the very young (0–4 years)—and in immune-compromised children. Diagnosis of TB disease in young children represents recent transmission of *M. tuberculosis*, and efforts should be made to identify and treat the source case.

The diagnosis of TB in children should be made based on careful and thorough assessment of all the findings from a careful history, clinical examination and relevant investigations, e.g., chest X-ray (CXR) and microbiologic tests. Most children with TB have pulmonary symptoms, and bacteriological confirmation of TB should be sought in all cases, through expectorated sputum samples or by gastric aspiration or sputum induction for those unable to expectorate.

The decision to treat a child should preferably be made by a Medical Officer after careful consideration; and once such a decision is made, the child should be treated with a full course of therapy. **A trial of treatment with TB medications is not recommended as a method to diagnose TB in children.**

The key risk factors for TB include:

- Household contact with a bacteriologically-proven case of TB
- Age less than 5 years – risk of developing TB disease is highest in very young children
- Immune status of child: immunosuppressive conditions make disease more likely. They include HIV infection, severe malnutrition and immune suppressive therapy such as corticosteroids
- Time since exposure/infection: vast majority of children who develop TB disease do so within the first two years.

The key features suggestive of TB are:

- Symptoms suggestive of TB
- Physical signs highly suggestive of TB
- A positive tuberculin skin test
- Chest X-ray suggestive of TB

Diagnosis of TB in children

The approach to diagnose TB in children follows the usual standard protocol in clinical practice. This includes:

- Careful TB screening using standard symptom screening tool at all entry points
- Careful history with high index of TB suspicion (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- **A positive tuberculin skin test (Where available and in the presence of a paediatrician)**
- Bacteriological confirmation
- Investigations relevant for presumed TB disease site
- HIV testing

A history of close contact – child living in the same household as, or in frequent contact with – a source of bacteriologically-proven TB strongly supports a diagnosis of TB in a child, particularly those younger than 5 years of age.

Active case finding is important in identifying children with active TB disease and in providing prophylaxis to asymptomatic children. The NTLP recommends the approach summarised below to improve childhood TB care in Lesotho.

- Screen all children under 5 years of age and adolescents who are household contacts of bacteriologically confirmed pulmonary TB cases.
- Screen all children under 15 years living with HIV
- Screen all symptomatic children (any age) who have contact with TB case.
- Effort should be made to detect the source case (usually an adult) and any other undiagnosed cases in the household when any child (aged less than 15 years) is diagnosed with TB.
- If a child presents with infectious TB, child contacts must be sought and screened, as for any infectious source case. Children should be regarded as infectious if they have laryngeal disease, sputum smear-positive pulmonary TB, or cavitary TB on CXR.

All children who have close contacts with TB patients should be considered presumptive for TB; therefore further TB investigations should be carried out

Clinical Presentation of Pulmonary TB

Infants with pulmonary TB commonly present with a history of nonproductive cough and difficulty breathing. Systemic symptoms such as fever, night sweats, poor weight gain or weight loss may also occur. They often present as a case of severe pneumonia with poor response to first-line antibiotic treatment.

Pulmonary disease and associated intrathoracic (hilar) adenopathy are the most frequent presentations of TB in preschool and school-aged children. Common symptoms of pulmonary TB in children in this age group include:

- Cough for 2 or more weeks that is not improving.
- Cough of any duration in a child living with HIV

- Fever for at least 2 weeks without other obvious etiology.
- Weight loss or failure to thrive (requires examination of the growth chart).

Although these symptoms are nonspecific, their presence supports a diagnosis of pulmonary TB. There are no specific features on clinical examination that can confirm that the presenting illness is due to pulmonary TB. However, persistent fever (temperature >38°C daily for more than 14 days), chronic cough that does not respond to antibiotics, and failure to gain weight are common.

The presentation of pulmonary TB in adolescents is similar to the presentation in adults. The typical symptoms of TB—cough lasting more than 2 weeks, fever for 2 or more weeks, weight loss, anorexia, malaise, night sweats, chest pain, and hemoptysis—are more likely to be present in adolescents than in children. However, cough and fever of any duration is presumptive TB in an HIV positive child.

Clinical Presentation of Extra-pulmonary TB (EPTB)

The clinical presentation of EPTB depends on the site of disease. The most common forms of extra-pulmonary disease in children are TB of the superficial lymph nodes, especially cervical and central nervous system. Neonates have the highest risk of miliary TB and TB meningitis. To diagnose EPTB, collect specimens for GeneXpert and/or culture from any site where disease is suspected. The most common extra-pulmonary specimens include tissue specimens such as lymph node or bone, cerebrospinal fluid, urine, bone marrow, and pleural fluid. Evidence is growing to utilize stool specimen in the diagnosis of childhood using GeneXpert. (Tissue specimen should be transported in saline)

In Every child suspected of having EPTB, perform investigations for pulmonary TB (sputum investigations, chest radiography) in addition to investigations dictated by the site of disease.

Very young children tend to have atypical presentation, changing to adult picture in older children

Diagnostic Tests

Collect sputum in children of all ages with presumptive pulmonary TB. Sputum specimens may be collected by means of expectoration, gastric aspiration, or sputum induction. While adolescents can produce expectorated sputum spontaneously, children younger than 6 years of age may be unable to do so. Sputum induction is the preferred method for collecting sputum from young children and those unable to expectorate. It has a higher diagnostic yield than expectorated sputum and is comparable to or better than inpatient gastric aspiration specimens. However, gastric aspiration should be used to obtain samples for testing in those unable to access sputum induction.
Diagnostic tests used in confirmation of EPTB will depend upon the site of disease.

Sputum samples for children are processed using the same procedures as adults. Please see Chapter 2: Diagnosis of Pulmonary TB for details.

Other Investigations for Childhood TB

Typical radiographic features of pulmonary TB: Most children with pulmonary TB will have abnormal findings on chest radiography. The most common chest radiograph findings in a child with TB disease include:

- Persistent opacification together with hilar or subcarinal lymphadenopathy.
- Advanced adenopathy causing bronchial compression leading to secondary infection or lung collapse.
- A miliary pattern of opacification.
- Other opacification that does not improve or resolve following a course of antibiotics.

Adolescents with TB generally present with typical adult disease findings of upper lobe infiltrates, pleural effusions, and cavitations on a chest radiograph. Adolescents may also develop primary disease with hilar adenopathy. Good-quality X-rays are essential for proper evaluation. A practical guide for interpreting CXRs has been developed.

Presumptive extra-pulmonary TB: In most of these cases, TB will be diagnosed from the clinical picture and confirmed by histology or other special investigations.

Table 27: Summary of investigations for extra-pulmonary TB in children

Anatomical Site	Recommended Investigations
TB adenitis (especially from the cervical region)	Lymph node biopsy or fine needle aspiration; sputum if coughing.
Miliary TB	Sputum and chest x-ray. Perform additional diagnostic tests as appropriate for associated signs and symptoms (e.g., lumbar puncture to test for meningitis).
TB meningitis	Lumbar puncture (CSF for white blood cell count with differential count); biochemical analysis for protein and glucose concentration, GeneXpert, and mycobacterial culture; chest x-ray; and sputum for GeneXpert.
Pleural effusion	Chest x-ray; pleural tap for biochemical analysis (protein and glucose concentration, white blood cell count, GeneXpert and mycobacterial culture); sputum.
Abdominal TB	Abdominal ultrasound and ascitic tap for white blood cell count total and differential; biochemical analysis for protein and glucose concentration, GeneXpert, and mycobacterial culture; sputum and chest x-ray if coughing.
TB of the spine/bones/joints (osteoarticular TB)	Spinal x-ray; joint tap for white blood cell count total and differential; biochemical analysis for protein and glucose concentration, GeneXpert, and mycobacterial culture; synovial biopsy; sputum if coughing.
Pericardial TB	Chest x-ray; chest ultrasound; pericardial tap for white blood cell count total and differential; biochemical analysis for protein and glucose concentration, GeneXpert, and mycobacterial culture; sputum if coughing.
Neonatal TB	Chest x-ray; lumbar puncture; CSF and gastric aspirates for GeneXpert and mycobacterial cultures; histopathology examination of the placenta for AFB

Anatomical Site	Recommended Investigations
	and granulomata; evaluation of the mother for TB.
Drug-resistant TB: any anatomical site	Mycobacterial culture and drug susceptibility testing of relevant specimens.

Other tests: HIV counselling and testing is indicated for all presumptive and confirmed TB cases as part of a standard package of comprehensive care.

Children living with HIV, and presenting with TB symptoms of any duration, should be considered as presumptive TB cases

Standard Case Definitions of TB in Children

The definitions used for adult TB also apply to children (see Chapter 1 for details). All children diagnosed with TB should be registered with the NTLP indicating the type of disease based on these standard case definitions.

TB treatment in Children

Treatment Basics

DOTS is applicable to all patients with TB, including children. The recommended treatment regimens for the TB diagnostic categories are generally the same for children as for adults. Children also receive treatment using fixed-dose-combination tablets. However, children require higher doses per kilogram body weight of individual medications to achieve treatment success. It is important to weigh the child at each clinical visit and adjust medication doses as needed.

Table 28 (a): Drug dosing for the treatment of TB in children

Drug	Daily dose and range mg/kg	Maximum daily dose
Isoniazid (H)	10 (7-15)	300 mg
Rifampicin (R)	15 (10-20)	600 mg
Pyrazinamide (Z)	35 (30-40)	2 g
Ethambutol (E)	20 (15-25)	2.5 g

Table 29: Recommended treatment regimens for children

TB disease category	Recommended regimen	
	Intensive phase	Continuation phase
Drug susceptible Tuberculosis (DS TB)		
All forms of pulmonary and extra-pulmonary TB *except TB meningitis and TB of the bones/joints*	2 months of daily RHZE	4 months of daily RH
TB meningitis TB of the bones/joints	2 months of daily RHZE	10 months of daily RH
Drug-resistant tuberculosis (DR TB)	See Chapter 9, "Drug-resistant TB"	

Treatment for all previously treated TB cases (relapse, treatment after default, treatment failure)

should be based on drug susceptibility test ie rapid molecular test such as genexpert

Miliary TB

Miliary TB in children presents a special case. Up to 30% of children with miliary TB will have central nervous system involvement. ALL children with miliary TB should have a lumbar puncture. If there are no abnormalities of the CSF, children should receive treatment as for pulmonary TB: 2 RHZE/ 4 RH. If there are any abnormalities of the CSF or if lumbar puncture cannot be performed but there is suspicion of meningeal involvement, the child should receive treatment for TB meningitis: 2 RHZE/10 RH.

Indications for corticosteroids

Corticosteroids (prednisolone) are recommended for all children with TB meningitis in a dosage of 2 mg/kg daily for 4 weeks. The dose should then be gradually reduced (tapered) over 1–2 weeks before stopping. The dosage of prednisolone can be increased to 4 mg/kg daily (maximum 60 mg/day) in the case of seriously ill children because rifampicin will decrease corticosteroid concentrations. As with adults, other complicated forms of TB, e.g. complications of airway obstruction by TB adenitis, and pericardial TB also require corticosteroid therapy.

TB Treatment dosing for children

The following dosing table provides information on the number of daily tablets needed to reach the proper dosing, based on the child's weight

Table 30: Weight-based dosing of anti-TB medications using paediatric fixed dose formulations
(2-25 kg body weight)

Weight (kg)	Intensive phase (2 months)		Continuation phase (4 months)
	RHZ (paediatric) 75/50/150 mg	**Ethambutol 100 mg**	**RH (paediatric) 75/50 mg**
2 - 3.9 kg	1/2 tablet	1/2 tablet	1/2 tablet
4 - 5.9 kg	1 tablet	1 tablet	1 tablet
6 - 7.9 kg	1.5 tablets	1.5 tablets	1.5 tablets
8 - 10.9 kg	2 tablets	2 tablets	2 tablets
11 - 14.9 kg	3 tablets	2 tablets	3 tablets
15 - 19.9 kg	4 tablets	3 tablets	4 tablets
20-24.9 kg	5 tablets	4 tablets *(or 400mg tablet)*	5 tablets

* Follow adult dosing for children weighing 25kg or above.

Previously treated TB Child Cases

Children previously treated for TB should be initiated on TB Treatment regimen based on results of molecular testing and/or DST. Sputum samples (expectorated or induced) or any other specimen taken for diagnosis need to be evaluated for drug resistance.

Administering Treatment and Ensuring Adherence

Treatment of childhood TB should be administered on an ambulatory basis. If it is not possible to ensure good adherence and treatment outcome on an outpatient basis, some children may require hospitalization for social or logistical reasons.
Children, their parents, other family members and caregivers should be educated about TB and the importance of completing treatment. The support of the child's parents and immediate family is vital to ensure a satisfactory outcome of treatment.

Simple, child-friendly TB treatment formulations offer the following advantages:

- The right medicines in the right doses to increase adherence and save more lives.
- Simplified fixed dose combination to ease drug administration, with fewer pills, simplified ordering and storage
- Taste good and simple to provide, easing the daily struggles of children, parents, and caregivers alike.

Follow-up of TB treatment in children

Ideally, each child should be assessed clinically at least at the following intervals: 2 weeks after treatment initiation, at the end of the intensive phase and every month until treatment completion. The assessment should include, as a minimum; symptom assessment, assessment of treatment adherence, enquiry about any adverse events and weight measurement.

Medication dosages should be adjusted to account for any weight gain.

Treatment adherence should be assessed by reviewing the treatment card. A follow-up sputum sample for smear microscopy at 2 months after treatment initiation should be obtained.

Follow-up chest x-rays are not routinely required in children, particularly as many children will have a slow radiological response to treatment. A child who is not responding to anti-TB treatment should be referred for further assessment and management. These children may have drug-resistant TB, an unusual complication of pulmonary TB, other causes of lung disease or problems with treatment adherence.

Adverse events

Adverse events caused by TB drugs are much less common in children than in adults. The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Serum liver enzyme levels should not be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (less than five times the normal values) is not an indication to stop treatment. However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs.

Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver functions have normalized. An expert (experienced in managing drug-induced hepatotoxicity) should be involved in the further management of such cases. If treatment for TB needs to be continued for severe forms of TB, nonhepatotoxic anti-TB drugs should be introduced (e.g. ethambutol, an aminoglycoside and a fluoroquinolone).

Isoniazid may cause symptomatic pyridoxine deficiency, particularly in severely malnourished children and HIV-infected children on ART. Supplemental pyridoxine (0.5–1 mg/kg/day) is recommended for all children receiving isoniazid.

Children with TB who are co-infected with HIV

Compared to HIV-uninfected children with TB, HIV-infected children with TB have worse outcomes of TB treatment and higher rates of mortality. This is likely due to a combination of factors, including severe immune suppression, co-existing malnutrition, HIV-related co-infections, Immune Reconstitution Inflammatory Syndrome (IRIS), and greater problems with adherence to treatment. The majority of deaths in HIV-infected children receiving treatment for TB occur in the first two months (intensive phase) of TB treatment.

Important treatment issues to consider:

- Start TB treatment first for all HIV-infected children with TB disease who are not yet on ART.
- Prescribe the same dosages and regimens of TB treatment to HIV-infected children with TB disease as are used in HIV-uninfected children.
- Start ART in all HIV-infected children with TB regardless of CD4 levels 2-4 weeks after TB treatment is started.
- Provide cotrimoxazole prophylaxis to all children with TB/HIV co-infection.

Most children with TB, including those who are HIV-infected, have a good response to treatment. Possible causes for failure, such as non-compliance with treatment, poor drug absorption, drug resistance and alternative diagnoses should be investigated in children who are not improving on TB treatment.

Children with TB and HIV who are receiving both ART and TB treatment need special consideration because of the potential drug-drug interactions between rifampicin and non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), the high pill burden, adherence concerns, and an increased likelihood of drug toxicity. Rifampicin reduces drug levels of NNRTIs and PIs when they are co-administered. This can lead to sub-therapeutic

ART drug levels and thereby increase the risk for developing ART drug resistance and ART treatment failure.

Efavirenz (EFV) is the preferred NNRTI to be used concurrently with rifampicin; however, it can only be used in children older than 3 years and weighing more than 10 kg. Lopinavir/ ritonavir (LPV/r) should be avoided when the child is taking rifampicin because the levels of LPV/r will decrease significantly, which can compromise virologic suppression. In situations where the use of nevirapine cannot be avoided, nevirapine should be used at a maximum dose (200 mg/m^2 twice daily). On ART initiation, do not use nevirapine lead-in dosing since it will lead to sub-therapeutic nevirapine levels and can compromise virologic suppression. For children under three years on an LPV/r regimen, substitute with nevirapine during TB treatment and resume LPV/r after completion of therapy. See ART guidelines for additional recommendations.

Table 31: Recommended ART regimens for infants and children receiving standard TB treatment

Status	Regimen
ART regimen in children receiving TB treatment	2 NNRTIs + EFV (for children >3 years of age and weighing >10 kg) 2 NNRTIs + LPV/r (for children <3 years of age and/or weighing <10 kg)
Children on TB treatment but not yet initiated on ART	For children <3 years of age and/or weighing <10 kg: initiate ABC/3TC/NVP For children >3 years of age and weighing >10 kg: initiate ABC/3TC/EFV
Children already on ART and started on TB treatment	Continue ART regimen For children <3 years of age and/or weighing <10 kg: Substitute NVP for LPV/r For children >3 years of age and weighing >10 kg: Substitute EFV for NVP or LPV/r

The effect of rifampicin on ART metabolism lasts for 2 weeks after rifampicin is stopped; hence, dose adjustments of ART should be continued for 2 weeks after completion of the rifampicin-containing therapy.

Contact Screening and Management

It is recommended that all household contacts be screened for symptoms of TB disease and TB preventive therapy offered to all children if they are aged less than 15 years or *living with HIV* in whom active TB disease has been excluded. Screening should be conducted using the screening tool recommended by the program.

Definitions used in contact screening

Source case: A case of pulmonary TB which results in infection or disease among contacts

Contacts for screening: All children under 15 years (whether sick or well)

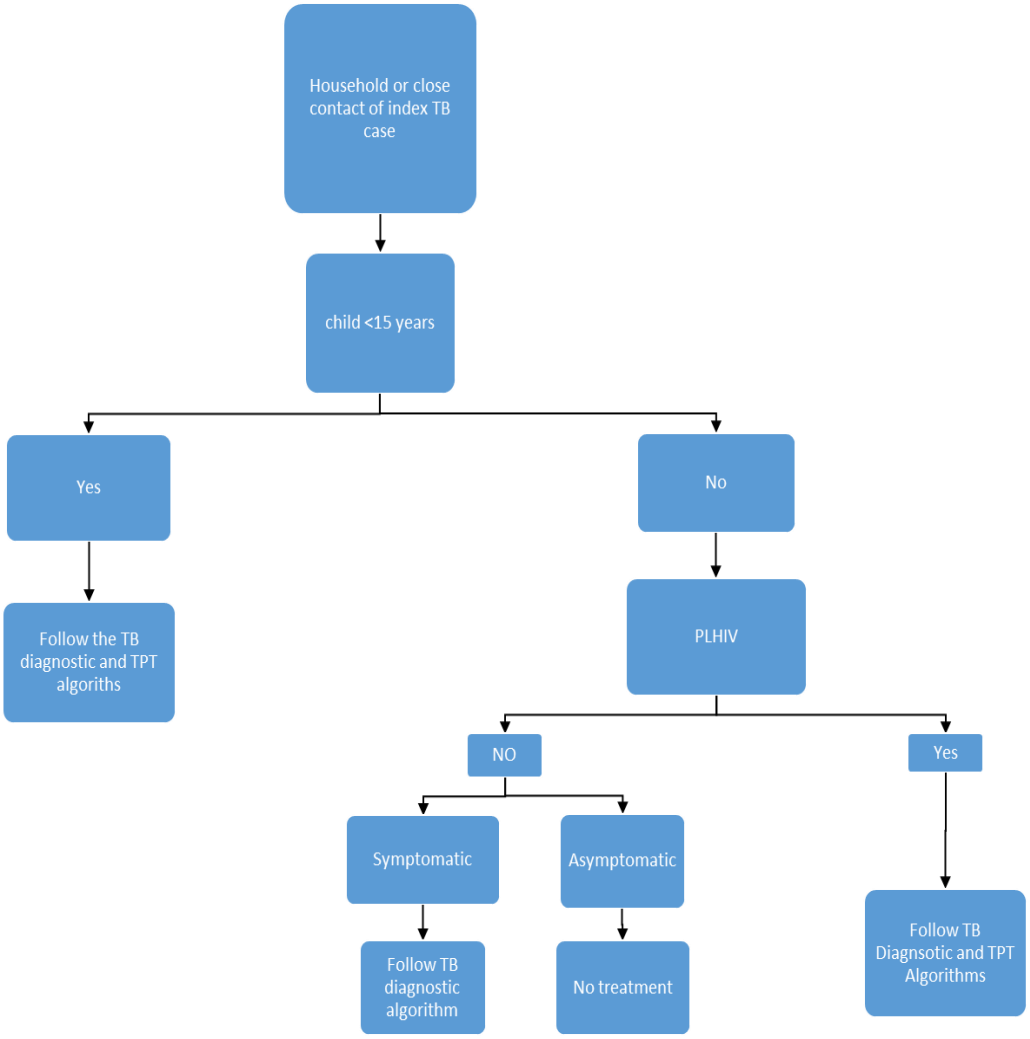
Close contact: Living in the same household as a source case (e.g. the child's caregiver) or in frequent contact with a source case

Assessment and Management

Contacts should be assessed clinically to decide whether the contact is well or symptomatic. Routine assessment of exposed contacts does not require CXR or TST. In line with WHO recommendations, contact investigation should be conducted for household and close contacts when the index case has any of the following characteristics:

- Bacteriologically confirmed PTB
- X/MDR-TB proven or suspected
- is a PLHIV
- is a child less than 5 years?

Figure 6: Approach to contact management



If the contact of a source case with pulmonary TB is symptomatic, then TB needs to be investigated as above irrespective of the contact's age.

Recommended prophylaxis for a healthy contact under 15 years is combination preventive therapy with Rifapentine and isoniazid (HP). Pyridoxine should be offered as well.

Follow-up should be carried out every month until prophylaxis is complete. If TB is suspected at initial assessment or at subsequent follow-up, diagnostic procedures should be followed as outlined in Chapter 3. Referral to a district or tertiary hospital may be necessary when there are uncertainties of diagnosis. Contacts with TB disease should be registered and treated, so should those who start TPT.

Special circumstances in child TB management

Child Contact is known to be HIV-Infected

If the child contact is below 15 years and asymptomatic, regardless of HIV status, TB preventive therapy should be considered. As with other patients who may be eligible for TPT, active disease should be ruled out before providing TB preventive therapy. HIV-infected children who have symptoms should be carefully evaluated for TB, and if found to have TB should be started on treatment

HIV infection of source case and contact

In Lesotho, where HIV prevalence is high among cases with pulmonary TB, if the source case is a parent, their children may be at risk of both TB and HIV infection. It is important to ask about the HIV status of the source case and child contact and offer HIV counselling and testing if unknown.

In settings of high HIV prevalence, it is recommended that all household and close contacts be counselled and tested for HIV.

Child Contacts of Infectious MDR-TB Cases

The only chemoprophylactic regimens to have been studied are based on isoniazid and, to a lesser extent, on rifampicin. Since by definition MDR-TB is resistant to both of these drugs, it is unlikely that use of these drugs to treat latent TB infection caused by an MDR-*M. Tuberculosis* strain will prevent the development of active TB disease. Close contacts of MDR-TB patients should receive careful clinical follow-up for a period of at least 2 years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended. On the basis of the currently available evidence, WHO does not recommend second-line drugs for chemoprophylaxis in MDR-TB contacts.

Management of a Baby Born to a Mother with Infectious Pulmonary TB

If a mother is found to have pulmonary TB, then the baby, and if possible, the placenta, should be investigated for evidence of congenital TB infection and the baby treated. Once the mother has been on treatment for two weeks, she is generally no longer infectious. If a mother has been on TB treatment several weeks before delivery, it is less likely that the baby will become infected. The risk is highest if a mother is diagnosed at the time of delivery or shortly thereafter.

A breastfeeding infant has a high risk of infection from a mother with bacteriologically-proven pulmonary TB, and subsequently, a high risk of developing TB disease. The infant should receive TB preventive therapy, followed by BCG immunization. Breastfeeding can be safely continued during this period.

Mycobacterium Other than TB (MOTT) OR Non-Tuberculosis Mycobacterium(NTM)

Introduction

Nontuberculous mycobacteria (NTMs) previously called MOTT refers to all species of the genus Mycobacteium, except Mycobacterium *tuberculosis* (TB). It may be non-pathogenic species, or it may indicate a true infection and should be further investigated to determine the species.

There are over 100 species of NTMs, most of which are environmental contaminants and do not cause disease in humans. A few can cause disease and most commonly are:

- *Mycobacterium avium*
- *Mycobacterium intracellulare*
- *Mycobacterium kansasii*
- *Mycobacterium abscessus*
- *Mycobacterium fortuitum*

Individuals at risk: People with lung damage from mining, previous TB or emphysema, are higher risk of developing pulmonary disease. Unlike TB, NTM cannot be transmitted from one person to another. Patients with advanced HIV infection (CD4 count of less than 50 cells) are at higher risk of developing disseminated infection with *Mycobacterium avium* complex (MAC) that may affect any organ.

Disease may present with same symptoms as disseminated TB. Gastrointestinal manifestations are the most common presentation in HIV-infected patients. Diagnosis is confirmed by blood culture or biopsy of the spleen, bone marrow or lymph nodes.

Clinical manifestations

Pulmonary manifestations account for 94% of cases of NTM but presentations may involve other areas such as skin, bones, and lymph nodes. The majority of cases are caused by MAC, followed by *M. kansassi*. The risk for infection increases in immune-suppressed patients or those with structural lung disease, particularly chronic obstructive pulmonary diseases (COPD) and bronchiesctasis. Parenchymal scarring and fibrosis from prior TB infection also increase risk of NTM. This often poses a challenge to health care workers as reactivation of TB should be considered in cases of suspected NTM infections.

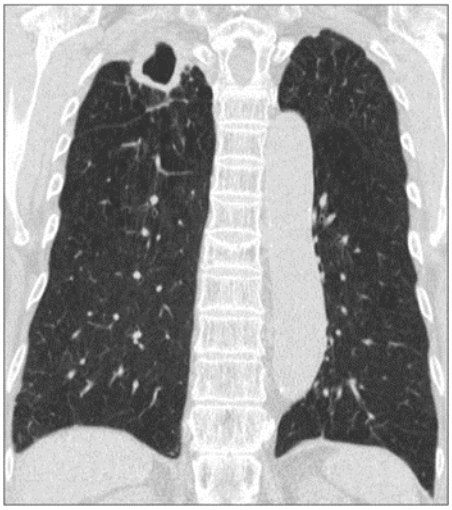
NTM often presents with symptoms such as chronic or recurring cough, sputum production, and dyspnoea. Other general symptoms like fever, fatigue, malaise, night sweats, and weight loss may occur. NTM may be similar to active pulmonary TB, especially with infections caused by *M. kansassi*.

Pulmonary NTM

Radiological imaging is important when NTM lung disease is suspected. The broad range of radiological patterns seen in NTM lung disease includes bronchiectasis, nodular lesions, cavitary lesions, and parenchymal consolidation. NTM lung disease has two major manifestations: fibrocavitary and nodular bronchiectatic forms.

Fibrocavitary disease

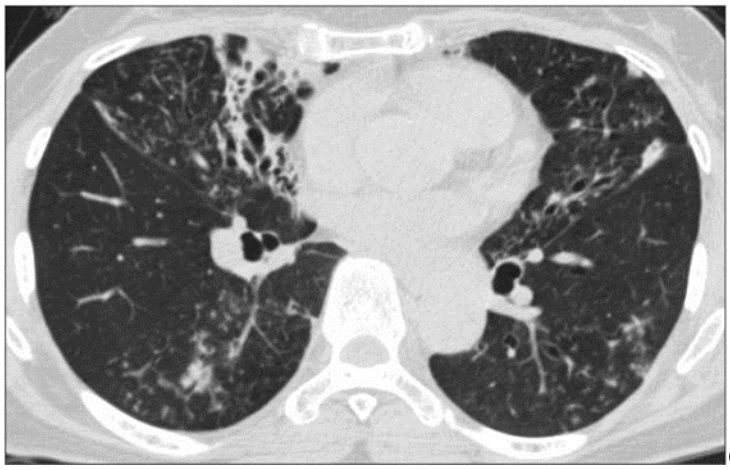
The fibrocavitary form resembles pulmonary TB and typically affects elderly men with underlying lung disease. This form is characterized by cavities with areas of increased opacity, usually located in the upper lobes. Pleural thickening and volume loss by fibrosis with traction bronchiectasis are frequent. Cavitation is the most typical radiologic feature in pulmonary TB; however, NTM lung disease tends to cause thin-walled cavities, often involving pleura without lymph node calcification, no atelectasis and usually progresses more slowly than pulmonary TB.


courtesy: Yon Ju Ryu

The fibrocavitary form of *Mycobacterium intracellulare* pulmonary disease in a 73-year-old male patient. Chest computed tomography shows a large cavity in the right upper lobe. Note the emphysema in both lungs

Nodular bronchiectatic disease

The nodular bronchiectatic form shows bilateral, multilobar bronchiectasis, especially in the middle and lower lung fields, with small nodules on chest radiography and high resolution computed tomography (HRCT). This pattern of NTM lung disease occurs predominantly in elderly non-smoking women without underlying lung disease, and appears more commonly in those with a thin body habitus. There is evidence for a possible role of NTM infection causing bronchiectasis. On the other hand, bronchiectasis can precede NTM infection in some conditions. A recent meta-analysis showed that the overall prevalence of NTM infection was 9.3% in patients with bronchiectasis. Clinicians should be aware that bronchiectasis and NTM lung disease are connected. Because of considerable overlap in common HRCT findings, it is difficult to differentiate species of NTM lung disease based on radiologic patterns.

 courtesy: Yon Ju Ryu

The nodular bronchiectatic form of *Mycobacterium intracellulare* pulmonary disease in a 70-year-old female patient. Chest computed tomography shows severe bronchiectasis in the right middle lobe and the lingular segment of the left upper lobe. Note the multiple small nodules and tree-in-bud appearances suggesting bronchiolitis in both lungs.

Diagnostic criteria for pulmonary NTM

The American Thoracic society diagnostic criteria developed and revised in 2007 recommends a combination of clinical, radiological and microbiological features. In order to make a diagnosis of pulmonary NTM infection all of the following must be present:

- Chronic pulmonary symptoms (cough for 2 weeks or more)
- Abnormal CXR
- At least 2 positive cultures from sputum for the same pathogenic NTM species

Disseminated NTM Infection

Disseminated NTM is a life-threatening illness that occurs almost exclusively in patients with advanced AIDS, and is rare in other forms of immune-suppression. Clinical findings include anaemia, fever, night sweats, weight loss, and hepato-splenomegally. In patients initiating antiretroviral therapy, disseminated NTM may occur as part of an immune reconstitution inflammatory syndrome (IRIS) and presents with painful suppurative lymphadenopathy, pulmonary infiltrates, and skin abscesses.

Successful treatment requires treatment of both HIV and NTM infections. Macrolides are the cornerstone of therapy for disseminated NTM. Although they are highly effective, resistance and treatment failure occurs in 50% of those receiving macrolides alone. Monotherapy is therefore contraindicated in disseminated NTM infections, and regimens should include ethambutol and rifampicin.

Mycobacterial lymphadenitis

Lymphadenitis is an uncommonly recognized manifestation of mycobacterial infection. The vast majority (80%) of culture-proven disease is caused by MAC.

Clinical manifestations of NTM lymphadenitis include non-tender, unilateral (95%) adenopathy is the most common finding and typically involves the submandibular, submaxillary, cervical, or preauricular lymph nodes. Although it is uncommon, affected nodes may rapidly enlarge, rupture, and form draining sinus tracts.

In suspected cases, excision biopsy is preferred as fine-needle aspiration or incision and drainage of the involved nodes may result in fistulae formation with chronic drainage. It is important to exclude *M. tuberculosis* as the cause of the lymphadenitis, especially in adults where greater than 90% of culture proven mycobacterial lymphadenitis is caused by *M. tuberculosis.*

The treatment of NTM lymphadenitis is complete surgical excision of the involved lymph nodes. Surgical resection is associated with a 95% success rate. In the absence of other sites of infection, medical therapy is rarely needed.

Bacteriology and culture for NTM

GeneXpert will be negative and isolation of NTM through culture and species identification is essential for the diagnosis of NTM lung disease. In case of pulmonary disease (the most common site of infection), bronchial cultures should be obtained. Patients should have at least 3 sputum specimens collected on separate days, and NTM should be confirmed by positive results in at least 2 of these 3 specimens. Bronchoscopic washing may be a useful diagnostic tool if available. Specimens obtained from biopsy (trans-bronchial lung biopsy, surgical lung biopsy, or excision biopsy from infected tissue) are also diagnostic if they produce isolation of NTM or show granulomatous inflammation on histo-pathology examination.

A single positive culture may be insufficient to provide a reliable diagnosis of NTM. Contamination is common, especially with sputum samples. Even rinsing of the mouth with tap water can cause false positive results. Likewise, cleaning the bronchoscope or culture plates with tap water can also result in contamination and false-positive results.

Therefore, a reliable diagnosis must be based on both a highly suspicious clinical picture and confident microbiologic studies. Without this, all positive cultures should be highly scrutinized, especially with less common species or in species known to be common contaminants (*M. gordonae, M. mucogenicum, M. terrae, M. kansassi, and M. abscessus).*

Remember to always apply the diagnostic criteria provided above for NTM disease

Classification of NTM

When solid culture medium is used, it is often possible to distinguish between the various types of clinically significant NTM based on growth patterns as followed:

Table 32: NTM classification

NTM Isolates	Possible Type
Form colonies on subculture in 7 days or fewer are referred to as rapidly growing mycobacteria	*M. abscessus*
That require more than 7 days to form mature colonies on subculture are termed 'slowly growing mycobacteria'	*M. kansassi* & *M. avium* complex
That change colour when exposed to light are called "photochromogens"	*M. kansassi*
That do not change colour when exposed to light are called "non-photochromogens"	*M. avium* complex

Differential diagnosis

TB is both much more common and is a higher health threat than NTM. Other pulmonary granulomatous diseases such as sarcoidosis and fungal infection can resemble NTM and should be included in the differential diagnosis. *Mycobacterium bovis* in people causes TB disease that can affect the lungs, lymph nodes, and other areas. Gastrointestinal disease can cause abdominal pain and diarrhea. Treatment is similar to *M. tuberculosis*.

Treatment of NTM disease

Not all patients with NTM disease need treatment.

Clinicians must make careful considerations about whether or not to treat their patients as the goals may differ from patient to patient: alleviation of symptoms or minimisation of disease progression.

Treatment regimens for NTM differ according to species. Several NTM species that cause human disease will respond to first line TB drugs. Second line TB drugs such as levofloxacine and amikacin may also be effective. Infection with *M. avium* or *M. intracellulare* requires rifampicin, ethambutol and clarithromycin.

Table 33: Treatment of NTM Disease

NTM Disease	Treatment	Special situations
Nodular bronchiectatic NTM	• Clarithromycin 1000 mg daily (or 500 mg twice a day) or azithromycin 250 mg daily • Rifampicin 10 mg/kg/day (maximum 600 mg/day) or rifabutin 150 to 300 mg • Ethambutol 15 mg/kg/day • Corticosteroid therapy may improve	Confirmed NTM by species • In *M. kansassi* infections, isoniazid should be added as *M. kansassi* is often susceptible. • In *M. abscessus* (rapidly growing) infections, cefoxitin should be added to the treatment.
Cavitary/fibronodular disease or severe symptomatic NTM	• Clarithromycin 1000 mg daily (or 500 mg twice a day) or azithromycin 250 mg daily • Rifampicin 10 mg/kg/day (maximum 600 mg/day) or rifabutin 150 to 300 mg. • Ethambutol 15 mg/kg/day • Amikacin or streptomycin for 2 to 3 months should be considered in severe cases.	

Treatment should be continued for **up to 12 months of documented negative sputum cultures.** Therefore, the typical duration of treatment is 18 to 24 months, but it can be longer for some. Surgical resection has been shown to improve outcomes in some patients with NTM infection and should be considered as an alternative to medical therapy.

CHAPTER 11 Monitoring and Evaluation

11.1 The basis for the M&E policy

The National TB Programme has aligned its efforts to the global actions to end the TB epidemic through its National Strategic plan (2018-2022). The M&E system's aim is to enable the National TB Programme to attain the goals and objectives set in the strategic plan which are aligned to the Sustainable Development Goals and the End TB Strategy targets. SDGs and the End TB strategy have very ambitious targets which require intensive and expanded TB Monitoring systems for sustained tracking of these targets and assessing progress and spearheading the required TB specific and multispectral interventions towards ending the epidemic.

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11.2 Programme Supervision

The NTLP will ensure sustenance of task-oriented supervision at all levels to increase the efficiency of health workers by developing their knowledge, perfecting their skills, improving their attitudes towards their work and increasing motivation. Additionally, the NTLP will provide technical supervision support to the district level centrally while the districts provide same to the health facility level.

Systematic supervision at the district level will focus on supporting the district officers in technical and managerial functions, while that of facilities will focus on identification of TB cases and administration of treatment including follow-up of cases.

Supervisory visits must be planned carefully. Before each visit, the supervisor will review the health centre's reports, the correspondence about the reports, the findings of the last supervisory visit and any corrective actions taken.

Supervision should be conducted using the appropriate tools that assess relevant tasks. The facilities should be notified in advance of the visitation date and purpose of the supervisory visit. The number of supervisory visits should be planned before the start of the fiscal year for inclusion in the annual-programme budget.

11.3 Programme Monitoring and Evaluation

The NTLP is responsible for monitoring health facility and community based DOTS services (case detection, treatment outcomes, availability of quality drugs, MDR-TB TB/HIV collaborative activities). The NTLP has developed service delivery registers for routine recording on TB services. Monitoring programme performance is carried out routinely in collaboration with implementing partners to ascertain that activities are accomplished as planned and to identify problems and formulate corrective measures. Monitoring should be conducted routinely with quarterly and annual assessments. Programme Evaluation should be conducted at the end of a plan period to assess progress towards operational targets and

epidemiological objectives. The evaluation should ensure measurement of all core programme indicators to assess progress in achieving targets and objectives.

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11.3.1 Programme Indicators

The NTLP encourages use of results generated by the M&E system for decision making to strengthen the effectiveness of the implementation of programme interventions.

Table 34: Standard indicators for monitoring and evaluation of the TB programme

Indicator	Description	Numerator	Denominator
Impact Indicators			
TB incidence rate	Estimated number of TB cases occurring per yea 100,000 population		
TB mortality rate	Estimated number of deaths due to TB (all cases) year, per 100,000 population		
Outcome indicators			
Case detection	New bacteriologically-confirmed TB cases detec (diagnosed and reported to NTP), among the new bacteriologically-confirmed TB cases estimated countrywide each year (number and percentage)		
Case notification rate of all f TB per 100,000 population - bacteriologically confirmed clinically diagnosed, new an relapse cases	Number of all forms of TB cases (i.e. bacteriolog confirmed plus clinically diagnosed) reported [in specified area] to the national health authority in year (new and relapse) expressed as a rate per 10 population	Number of all forms of TB case bacteriologically confirmed plus clinically diagnosed) reported [i specified area] to the national h authority in the past year (new a relapse)	Total population in the spec area x 100,000
Treatment success rate (all fo	Percentage of all forms TB cases (bacteriologica confirmed and clinically diagnosed) successfully (cured plus treatment completed among all forms cases notified during a specified period. Successf completion entails clinical success with or witho bacteriological evidence of cure (number and percentage)	Total number of all forms of TB cured plus completed	Total number of all forms o cases notified

Treatment success rate (bacteriologically confirmed)	Percentage of new and relapse bacteriologically confirmed TB cases successfully treated (cured p treatment completed among new and relapse bacteriologically confirmed TB cases notified du specified period. Successful completion entails c success with or without bacteriological evidence (number and percentage)	Total number of new and relaps bacteriologically confirmed TB cured plus completed	Total number of new and re bacteriologically confirmed cases notified
Identification of Infectious TB cases			
Proportion of bacteriological positive	# or percentage of persons found to be bacteriolo confirmed cases of TB, among persons identifiec presumptive TB cases during a specified time pe	Total number of presumptive TI that are bacteriologically positiv	Total number of presumptiv cases
Prevention in Under five contacts of TB patients			
Number of children under 5 contact with TB patients who treatment for latent TB infec (TB preventive therapy)	Number of children under 5 in contact with TB p who began treatment for latent TB infection (TB preventive therapy)	Number of children <5 in conta TB patients who began treatme latent TB infection (TB prevent therapy)	N/A
Intensified case finding among HIV-infected persons:			
Proportion of HIV-infected p screened for TB	Number of HIV-infected persons receiving HIV treatment and care services, who were screened f symptoms expressed as a proportion of all HIV-i persons attending HIV treatment and care service	**Numerator:** Number of HIV-infected persons seen at HIV treatment and care services who were screened for TB sympt over a given time period	
		Denominator: Total number of HIV-infected persons seen a treatment and care services over the same time period.	
Proportion of HIV-infected p with TB	Number of cases of newly-diagnosed TB identifi HIV-infected persons attending HIV treatment ar services, expressed as a proportion of all HIV-inf persons attending treatment and care services.	**Numerator:** The number of cases of newly-diagnosed TB identified in HIV-infected persons attending HIV treatment a services over a given time period	
		Denominator: Total number of HIV-infected persons attend HIV treatment and care services	

		over the same time period
Prevention of TB disease among HIV-infected persons		
Proportion of eligible HIV-in persons on latent TB Preven treatment	Number of eligible HIV-infected clients who are treatment for latent TB infection (TB preventive therapy) expressed as a proportion of the total nu eligible HIV-infected people	**Numerator:** Total number of eligible HIV-infected clients i active TB has been excluded who start (given at least one do treatment of latent TB infection
		Denominator: Total number of eligible HIV-infected client
Prevention of HIV in TB patients		
Proportion of TB patients counselled and tested for HI	Number of registered TB patients who are tested HIV as a proportion of the total number of regist cases	**Numerator:** Total number of registered TB patients who are for HIV during their TB treatment during a given time perio
		Denominator: Total number of registered TB patients over same time period.
Proportion of TB patients tha positive for HIV.	Number of registered TB patients who test positi HIV, expressed as a proportion of the total numb registered TB patients who are tested for HIV.	**Numerator:** Total number of all TB patients registered over time period who test positive for HIV during TB treatment
		Denominator: Total number of TB patients registered over same time period who are tested for HIV
Prevention of opportunistic infection in HIV-infected TB patients		
Proportion of HIV-infected T patients on CPT	Number of HIV-infected TB patients who are giv least one dose of CPT during TB treatment as a proportion of the total number of HIV-infected T patients.	**Numerator:** Number of HIV-infected TB patients, registere given time period, who are given at least one dose of CPT du their TB treatment
		Denominator: Total number of HIV-infected TB patients re over the same given time period
HIV Care and Support for HIV-infected TB patients		
Provision of anti-retroviral therapy for TB patients		

Proportion of HIV-infected T patients receiving ART	Number of HIV-infected registered TB patients v initiated or continue previously initiated ART , a proportion of all HIV-infected registered TB pati	**Numerator:** All HIV-infected TB patients, registered over a time period, who receive ART during intensive phase (are in or continue previously initiated ART)	
		Denominator: All HIV-infected TB patients registered over same given time period	
Notification among High risk groups			
Number of TB cases (all forr notified among key populatic high risk groups	Number of TB cases (all forms) notified among k populations/ high risk groups (other than prisone miners, ex-miners, household members of miners ex-miners, HCW, factory workers, or other relev KAP groups)	Number of TB cases (all forms) notified among key populations risk groups	N/A

11.4 Reporting and Recording system

In order to provide superior care to TB patients, health facilities should keep records on each patient, with periodic reporting of case-finding and treatment. This is essential to ensure that the patient is correctly treated and that adequate supplies of essential materials are provided. By routinely collecting and reviewing information, any problems associated with the management of the patient is more easily identified. The documents used to record and report patient care should be simple, clear and kept to the absolute minimum that is required for adequate care. The following description provides a guide for the recording of patients as it appears in the health facility and comprises the minimum number of records and reports necessary to ensure the proper care of the patients.

Table 35: Recording and reporting formats used in the National TB Programme

S/No.	M&E format	Data requirement	Level	Responsible	Frequency entry
1	TB Screening tally	Records clients screened for	Health facil	General Health staff	Daily
1	TB Presumptive an detection register	Records of clients with signs symptoms of TB	Health facil	General Health staff	Daily
2	Sputum Examinatio request form	Results of sputum examinati	Health facil Laboratory	General Health staff and labora personnel	Daily
3	TB Laboratory regi	Results of specimen examina	Laboratory	Laboratory per	Daily
5	TB facility Treatme Card	Patients' treatment records a progress	Health facil	General Health staff	Daily
	Patient Treatment C	Patients' treatment progress	Home	Patient/DOT supporter	Daily
6	Appointment Book	Patient appointments	Health facil	General Health staff	Daily
7	TB referral/ Transf	Patient's up to date treatmen	Health facil Home	General Health staff	Based on n
8	TB Treatment Regi	Records of all TB cases	Health facil	General Health staff	Daily
	Quarterly report on case detection (Cor tracing and screeni	Report on clients screened fo and contact tracing		General Health staff	Quarterly
10	Quarterly report on Case notification	Report on TB cases detected quarter by category.	health facili National	General Health staff	Quarterly
11	Quarterly Report o surveillance of DR	Report on drug susceptibility patients notified in a quarter	Health facil	General Health staff	Quarterly
12	t Quarterly report o treatment outcomes	Report on treatment outcome cases started on treatment 12	Health facil	General Health staff	Quarterly

S/No.	M&E format	Data requirement	Level	Responsible	Frequency entry
		months earlier.			
13	District TB drugs o form.	Quarterly district or national utilization and request	Health facil	General Health staff	Quarterly

10	District Quarterly Report on TB Case finding form	Report on TB cases detected in a quarter by category.	District/ National	District TB Coordinator	Quarterly, Annual
11	District Quarterly Report on Sputum Conversion form.	Report on treatment outcome of TB cases started on treatment 3-6 months earlier.	District/ National	District TB Coordinator	Quarterly, Annual
12	District Quarterly TB Cohort Report form.	Report on treatment outcome of TB cases started on treatment 12-15 months earlier.	District/ National	District TB Coordinator	Quarterly, Annual
13	District TB drugs order form.	Quarterly district or national drug utilization and request	District/ National	District TB Coordinator	Quarterly, Annual

CHAPTER 12 TB Medicines Supplies and Logistics Management

Rationale

Availability of TB drugs and other supplies is essential for provision of effective TB services on a continual basis, and hence must be procured and distributed in adequate quantities, at the appropriate time from credible WHO prequalified manufactures. Non-availability of anti-TB Medicines to a patient at any time is a serious weakness in a TB programme and can contribute to the emergence of TB drug resistance. Within the context of TB control, supply and logistics refers to the maintenance of a system that guarantees uninterrupted supply of anti-TB medicines, laboratory reagents and supplies, reporting and recording forms.

TB drugs are procured by the National Drug Service Organization (NDSO), and almost all are currently being procured from the GDF. The Programme uses FDCs for first line drugs. Supply to districts and peripheral is through a pull system based on monthly patient enrolment statistics plus a 50-100% buffer depending on availability of storage space. Management of anti-TB medicines are currently centralized and operate outside the general primary health care system.

Centrally the NTP Manager coordinates procurement of the TB Medicines through support from partners such Global Drug Facility (GDF). The District TB Coordinators in collaboration with the Pharmacist /Pharmacy Technician take responsibility for the provision of an uninterrupted anti-TB medicine supply.

Estimating Drug Needs and Preparing Procurement Plan

Before estimating drug requirements, the lead time (length of time between placing an order and receiving it) must be known. If the lead time is 6 months or more, the procurement plans should cover the drug needs for one year plus the reserve stock. Estimates of drug requirements are based on the expected number of cases to be treated using the recommended standard regimen for treatment.

Estimate the expected number of cases in each treatment category and the number of patients' kit and other FDCs required for next quarter

Sufficient stock of anti TB Medicines should be available in the country for all TB patients expected to be started on treatment during a whole year. Drug supply to the district level will be carried out on quarterly basis based on notification. The number of patients detected in a particular quarter is used to determine the requirements for the next. The District TB Coordinator in collaboration with the Pharmacist/Pharmacy Technician will determine these numbers from records of current cases and will order medicines for the facilities to meet the expected need including a provision for buffer stock. The reserve stock allows for possible increases in the number of cases and extra supplies in case of delay in drug delivery. These regimens are packaged in patient kits, which make calculation and accounting easy.

GDF Patient Kits

Lesotho uses FDCs for first-line TB treatment because these medicines significantly reduce a patient's pill burden and can significantly improve adherence levels.

Table 36: Advantages and limitations of patient kits

Advantages of Patient Kits	Limitations
Standardized treatment: Allows health workers to select a single container that has the predetermined medicines, strengths, and quantities (the TB patient kit for administering to the patient), limiting confusion and wastage *Quantification for procurement or ordering:* Improves ease of estimating medicine needs whereby 1 patient = 1 patient kit *Distribution of TB medicines:* Improves ease of logistics in that fewer items are being transported *Stock management and inventory control*: Improves ease of managing stocks and documentation of stock movement because one product is handled *Patient adherence:* Whereas medicine stock-outs cause patients to lose confidence in the health system, the patient kit assures the TB patient that his or her medicines will be available from start to finish of treatment. In addition, the patient may feel ownership of the patient kit and will likely complete the full course of treatment since he or she can see how many	Larger storage space may be needed in central and local warehouses Personnel should be trained in the adjustment of kits according to body weight, inventory methods, and repacking If TB packs are reconstituted, loose medicines must be collected, packing materials must be available, an area should be available for reconstitution in the warehouse, and procedures such as "Good Storage

Advantages of Patient Kits	Limitations
medicines must still be taken to achieve cure during visits to the health centre or dispensary	Practices" should be in place and followed

Management of patient kits is as follows:

- All health facilities should have patient kits in store to cater for at least two New TB Treatment regimens and one Retreatment regimen
- *In-patients.* The personalized patient kits should be supplied to the Ward Nurse who will dispense to the patient on daily basis. When a patient is discharged before completing treatment, the Patient Kits should be transferred to the nearest Health Facility
- *Patients who die, are lost-to-follow-up or fail treatment:* The remaining complete blisters will be put in a "Supply Box", for re-packaging of a new Patient Kit. The repackaging is done by the Pharmacy staff, and the number of repackaged Patient Kits is entered on the Quarterly Patient Kit Ordering Form
- *Patients who are transferred:* The patient kit follows the patient. Advantage is the transparent accountability, because Patient Kits orders are based on registered cases, which exclude transfers in. When a patient is diagnosed in a health facility and subsequently transferred to another near home, the TB Coordinator fills in a transfer form for the patient. The patient collects blisters from the "supply box" to cover the period for him/her to reach the health facility while the kit is transferred to the clinic
- *Quarterly Patient Kit Ordering Form:* The form is filled out quarterly within one week after the quarter end, together by Pharmacy staff and TB Coordinator or Officer. The form is sent to the NTP, which then forwards a complete set of Order Forms to NDSO. NDSO will then take care of distribution to all Districts

For patients weighing >70kg, additional FDCs will need to be added to the kits.

Some single-formulation tablets are needed for patients who develop side effects on the fixed dose combinations.

There are no specific pre-packaged kits for Retreatment regimen.

Adjustment of the GDF patient kits: The patient kits for **New TB Treatment** regimen include: 2[RHZE]/4[RHE].

- For 2 months intensive phase patient kit contains 6 blisters of RHZE in FDC.
- For 4 months continuation phase the patient kit contains 12 blisters of RHE in FDC.

The kits are prepared for the middle weight patient, one that weighs between 40-54 kg., since most TB patients weigh within this range when they begin treatment. Note that treatment regimen requires 28 doses to be given in a month and that blisters for all medicines contain 28 tablets.

Separate containers should be prepared and labelled "**Supply Box RHZE**" "**Supply box RHE**" and "**Supply Box RHE**," to place the blister sheets removed from a patient kit for a lighter weight patient or those who may been lost-to-follow-up or died. These same supply boxes should be used to get the additional blister sheets needed for heavier patients. When a supply box is empty and additional tablets are required for a patient, the supply box should be replenished with a new patient kit from which the required tablets are obtained. Discard the now empty patient kit unless required to keep it for accountability purposes to be checked by the district supervisor.

Note: When using medicines from the supply box always check the expiry dates and never give expired medicines to patients; if expired, remove the medicines and store away from the un-expired medicines for later disposal.

Always follow the FEFO Rule (First Expiry – First Out): always issue that stock which will expire first.

Table 37: Adjustments for new TB treatment regimen

Patient weighs	RHZE blisters	RHE blisters
30-39 kg	remove 2 blister sheets	remove 4 blister sheets
40-54 kg	no changes	no changes
55-70 kg	add 2 blister sheets	add 4 blister sheets

Table 39: List of anti-TB medicines available in Lesotho

First line	Formulation	Second line	Formulation
[RHZE] adult	Fixed-dosage combination tablet: [R150mg;H75mg;Z400mg;E275mg]	**Ethionamide/Prothionamide**	250mg tablet
[RH] adult	Fixed-dosage combination tablet: [R150mg; H75mg]	**Levofloxacin**	250mg tablet
[RHE]adult	Fixed-dosage combination tablet: [R150mg;H75mg;E275mg]	**Cycloserin**	250mg tablet
[RHZ] child	Fixed-dosage combination sachets: [RR60mg; H30mg; Z150mg]	**Kanamycin**	1g powder for injection
[RH] child	Fixed-dosage combination sachets:	**Capreomycin**	1g powder for

	[R60mg;H30mg]		injection
Ethambutol	400mg, 100mg tablet	**Moxifloxacin**	400mg
Isoniazid	100mg dispersible, 300mg tablet	PAS	4g sachet
Rifampicin	450mg, 150mg capsule/tablet		
Pyrazinamide	500mg tablet		

Role of Central Pharmaceutical Unit of the NTP:

- Ensuring availability of all anti-TB medicines at all times by strengthening medicine supply management
- Coordinating with the GDF through annual applications for free or partial grants and ordering
- Strengthening the quality assurance system to ensure that safe and high-quality medicines are supplied
- Promoting rational use of anti-TB medicines by prescribers, dispensers and clients
- Training on new guidelines and use of anti TB Medicines

Role of the District TB Coordinator/ Officer in the management of anti-TB medicines:

- Registering and notifying all forms of TB
- Ensuring all prescriptions conform to national guidelines and are reflected in the registers and the TB treatment cards
- Ordering anti-TB medicines from the pharmacy every 1-3 months
- Supervising packaging of medicines for peripheral clinics and DOT points and provision of DOT
- Ensuring continuous supply of medicines and proper storage as well as reporting on usage of medicines
- Informing the pharmaceutical staff of new cases and their regimens promptly so that the pharmacy can organize the medicine for the newly registered cases

Role of the Pharmacist/Pharmacist Technician in the management of anti-TB medicines:

- Supplying medicines to the TB clinic or TB ward as requested
- Assisting the TB Coordinator in forecasting needs
- Ordering medicines from the relevant distribution channels
- Preventing stock-outs

Role of treatment supporters/VHW management of anti-TB medicines

- Escorting TB Patients for follow-up visits to the clinic/TB nurse or collect supply if patient is unable to attend clinic
- Ensuring that medicines get to the patients on time.
- Observing patients swallowing their prescribed medicines.
- Reporting any problems to the TB Coordinator/ Health Nurse or Doctor

Logistics for laboratory materials

The laboratories and health facilities require an adequate supply of sputum containers to collect and transport sputum specimens. All health facilities should have sputum containers for

presumptive TB patients. The laboratories also need a regular supply of slides, reagents and other materials to perform the required tests.

Estimating Laboratory Materials Requirements

The laboratory supplies required for GeneXpert examinations are estimated on the basis of the expected prevalence of TB among the respiratory symptoms of presumptive cases who attend health care facilities. Generally, prevalence of bacteriologically confirmed cases among Presumptive Pulmonary TB patients at health facilities ranges from 25 -30%.

Sputum containers are needed to identify and investigate Presumptive TB cases and to follow-up patients. A shortage of sputum containers can constitute a major barrier to the TB diagnostic process and must be avoided.

Estimation of the quarterly requirements for sputum containers is based on the expected number of sputum examinations conducted for diagnosis plus the expected number conducted for follow-up. Estimates can be based on the number of new cases treated in the previous quarter.

The National TB Reference Laboratory is responsible for determining and advising on the specifications for laboratory equipment and supplies.

Suggested specifications for sputum containers are:

- The container mouth should measure at least 50mm to facilitate sputum collection
- The container should have a watertight screw cap permitting full hermetic closure to prevent leakage during transportation
- The container should be made of disposable material (plastic) that can be destroyed easily by burning
- The container should be made of translucent material so that the level of sputum in the interior can be clearly seen

References:

1. WHO 2007: Improving the diagnosis and treatment of smear negative and extrapulmonary TB among adult and adolescents.
2. G.L. Mandel; Principles and practice of infectious diseases 6th edition (2005):2857-2883
3. WHO 2010: Treatment of TB guideline 4th edition.
4. WHO 2017: Guidelines for Treatment of DS TB and patient care update
5. WHO End TB strategy
6. WHO 2018: Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management
7. GLI 2017: Planning for country transition to Xpert® MTB/RIF Ultra cartridges